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ANALYSIS OF RETINAL FUNCTION FOLLOWING LASER IRRADIATION

ANNUAL/FINAL REPORT

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DAVID O. ROBBINS

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Ohio Wesleyan University
Delaware, Ohio   43015

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David O. Robbins

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Ohio Wesleyan University
Delaware, Ohio 43015

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Exposure of the fovea to single or multiple pulses of coherent light (532 nm) can produce both transient and permanent changes in the eye's ability to resolve fine spatial detail. The immediate effects for extended duration exposures (>50 msec) are often large, producing acuity deficits as great as 90% of its pre-exposure level. The size of these deficits often reflect a total loss of foveal functioning although, depending upon the energy and duration of the exposure, these changes are reversible. Permanent changes in acuity can be noted in the absence of gross morphological damage and at power densities below the ED_{50} level provided the area of involvement is large. On the other hand, at power densities above the ED_{50} level, little if any permanent or consistent visual deficits are noted if the damage is restricted to relatively isolated areas within either the foveal or parafovea. Multiple pulses which increase the area of total involvement are more effective in permanently shifting postexposure acuity than are the single pulse conditions. Cumulative effects of repetitive exposures separate in time by as much as several days are possible. The exact parameters of any observed loss in visual performance of course is dependent upon the discrimination task and its ability to depict subtle changes in the retina mosiac.

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FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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INTRODUCTION

The design and performance characteristics of lasers in recent years has greatly increased the application of these devises both within the military and elsewhere. New lasers are capable of delivering shorter pulses of non-ionizing radiation that are significantly higher in energy density than their older counterparts. Their output spectral range has been increased to include the ultraviolet and infrared regions of the spectrum in addition to those in the visible spectrum. As a consequence, eye hazards associated with intentional or accidental exposure are likely to become an increasing biomedical problem.

Any bodily tissue which can absorb incident light has the potential of being altered regardless of how brief the exposure may be. The induced damage to any biological tissue produced by this absorption may be the result of thermal, mechanical or photochemical alterations to the tissue. The specific damage mechanism that results is dependent upon the operating characteristics of the laser (i.e., its output wavelength, energy, and duration) as well as the absorption characteristics of the exposed tissue. Ultimately, however, the tissue's damage threshold is dependent upon the interaction of radiometric and biological factors. Radiometric factors influence the amount of energy produced, absorbed and dissipated over time while biological factors which determine the physical abilities of the tissue to withstand the damage inflicted and generate the necessary repair mechanisms to survive. As early as 1970, it became clear that the establishment of a single maximum permissible exposure (MPE) for all exposure conditions was not possible and a sliding scale of values needed to be established much like those derived for chemical toxicity (1).

Light overabsorption can result from a brief, single exposure, from multiple exposures to energy levels which individually produce no observable consequences, or from chronic exposure conditions where the tissue's natural repair mechanism becomes fatigued. At the present time established MPE's (maximum permissible energy) appear insufficient to provide reasonable protection from chronic exposures. Photosensitive reactions can fatigue the tissue's natural repair process (2) and may only marginally protect one from the cumulative influences of multiple exposures within a more restricted time period where the energy densities of the exposures are within the intermediate zone between being clearly safe and clearly hazardous.

The eye, a delicate organ and photodetector by nature, is especially vulnerable to damage from light absorption. The specific location of the damage within the eye is determined primarily by the exposure wavelength and can be restricted to the cornea or to the electrochemically active retina. Damage to the cornea can be extremely painful and can alter the transmission properties of the cornea thereby indirectly altering vision. Damage at the retinal level, on the other hand, typically produces more immediate and significant alterations in visual sensitivity which can be either temporary or permanent in nature.

For the soldier, even temporary visual impairment could jeopardize the individual's ability to complete a visual-motor response and thereby imperil either the soldier or follow soldiers from the successful completion of a mission. Under typical field conditions, the brevity and distance of probable exposures as well as the optical properties of the eye would likely produce a retinal exposure of about 50 microns in diameter. If the human observer happened to fixate on the laser source, its image would likely fall on the fovea, the portion of the retina that mediates maximal visual acuity and color vision. Even in the unlikely event that the soldier is exposed to only a single 15 nsec pulse, its intense energy would produce an immediate, although perhaps temporary, blind spot which could seriously disrupt detection of a critical detail in a complex visual field. Repetitive Q-switched exposures or extended-source exposures from Q-switched or continuous beam lasers would likely produce damage extending over a wider retinal area which would further decrease visibility by the human observer. Hence, the establishment of safe operating guidelines, development of protective devices against accidental exposure, and the determination of the visual consequences of any type of retinal exposure must remain a high priority in any laser program.

Historically, attempts to derive the MPE and laser occupational exposure limits (EL's) employed only traditional morphological criteria

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which included fundoscopic and histological verification of tissue damage. As early as 1968, threshold limit values (TLV's) were established for the US Army and US Air Force by the American Conference of Governmental Industrial Hygienists (ACGIH) using these criteria. Controversy surrounding these standards as well as more current ones center on the issues of extrapolation across different laser systems and across animal/ human species as well as the degree to which added safety should be incorporated into the limits because of the uncertainty in the data (1). Furthermore, these limits do not directly consider the functional consequences of any induced damage nor the fact that acute physical effects could be delayed, microscopic, or cumulative in nature.

As a first step in resolving these controversies, the minimal energies necessary to elicit ocular damage must be derived using a wider variety of exposure conditions that explore delayed or cumulative consequences of repetitive pulses. These thresholds could be determined by traditional morphological means including microscopic analyses of retinal changes or they could be defined in terms of functional changes (electrophysiological and behavioral) within the visual system. In many ways the latter criteria may be the most important criteria for military planners since these standards relate more directly to the ability of an operator to maintain visually-guided behavior. Furthermore, legal liability for treatment and provisions for disability will ultimately depend upon the demonstrated presence of perceptual dysfunctions rather than morphological alterations.

The mandate to reevaluate existing safety standards continues even if one were to argue for the sole use of traditional morphological assessment criteria. Technological advances in histology and electrophysiology have greatly improved the analytical methodology for assessing retinal morphology and function. These procedures have shown that moderate as well as intense light can produce permanent changes in retinal morphology (3, 4, 5). As a result, predicted and observed damage thresholds have become inconsistent, in part due to the differential sensitivities of the various assessment techniques employed. In addition, inconsistencies have resulted from the growing diversities within the delivery systems of newer laser devices.

Histopathological examination (6,7,8,9) of exposed retinae reveal damage at lower exposure levels than are typically observed by traditional ophthalmological examinations alone especially when the area of retinal involvement is restricted. The photoreceptor outer segment has become the primary damage site (10,11) especially when low energy exposures are employed. The isolation of initial damage at the receptor level is significant since this is also the site of the initial transduction of radiant energy to electrochemical energy, a process that is fundamental to the whole basis for vision. Since the visual receptor cell is a photochemical device, photochemical changes associated with abnormally high levels of light absorption might also lead to damage thresholds not easily depicted by morphological criteria alone regardless of how molecular those measures may become.

Given these facts, the employment of functional criteria might be more relevant in determining safety thresholds and might produce even lower energy limits upon which to base our standards. As with other established criteria, however, thresholds for permanent shifts in visual sensitivity have varied depending upon the visual task used. Changes in the luminance, wavelength, and contrast of test targets have yielded various damage thresholds although most are still considerably lower than those derived using traditional morphological criteria. Relatively recent improvements in the behavioral techniques for assessing functional impairment (12) have even further lowered the damage threshold and have provided the opportunity for the examination of the transitional zone between temporary and permanent shifts in visual acuity. The elimination of anesthesia for placement of acute laser exposures, which was a part of all previous behavioral studies (11, 13, 14, 15, 16), has allowed for the measurement of transient acuity changes during the initial phases of the recovery process and the exploration of power levels below those that produce permanent shifts in visual functioning. The present report utilizes this methodology for exposing awake, task-oriented animals.

Since the damage mechanism for relatively low energy exposures is likely to be influenced strongly by photochemical alterations (4), the quantal efficiency of the particular wavelength used becomes a critical factor in influencing the severity of the damage (17). Other factors include the thermal properties of the eye (e.g. diffusivity), retinal position, and the energy density, duration, and spatial extent of the exposing beam. Because there are so many factors

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involved, no clear boundaries exist for each type of damage mechanism and, in fact, there are thought to be several transitional zones where more than one mechanism may be operating. For instance, it has been suggested that thermally enhanced photochemical effects may occur when tissue temperature rises alone which are not adequate to cause thermal injury.

Photochemical alterations in the retinal biochemistry prevent the natural cyclic mechanisms of the photoreceptors to function normally. Several chromophores may be involved. The effects of these alterations may develop more slowly (18, 19) then the more immediately observable consequences of thermal or mechanical injury. To date, there has been no systematic examination of any differential effects these damage mechanisms may have on visual sensitivity.

It has been shown that thermal damage occurs when the radiant energy of incoming photons is absorbed by biomolecules (mainly melanosomes of the retinal pigment epithelium or RPE). This energy is converted to heat, resulting in a temperature rise in the neural retina, RPE, and/or choroid. Even slight temperature increases can prompt the denaturation of proteins with loss of tertiary structure and possible polymerization. Temperature increases of greater than 10° C may cause irreversible denaturation, with permanent loss of tissue function. This thermal mechanism is a rate dependent process (20, 21), a fact shown both empirically (20) and theoretically (23). Birngruber (24), for example, demonstrated that the degree of temperature rise is a function of the energy density, duration, and wavelength of the exposing light as well as a function of the optical and thermal properties of the biological tissue. Because of the time-energy interdependence, no one threshold can be established, but generally thermal injury cannot occur for exposure durations of less than a microsecond. Theoretical models have also been developed and empirically confirmed (25) predicting a direct relationship between spot size and temperature rise. Generally, the larger the retinal image of the beam, the lower the power density needed to form a threshold lesion. Thermal lesions are generally homogeneous due to significant thermal diffusion, although they may be smaller than the laser beam size since maximum temperature and therefore maximum damage occur in the center of the laser beam image.

Mechanical damage occurs in the retina when high power, short duration exposures cause the propagation of sonic waves in the ocular tissue. The pressure front generated within the RPE and/or choroid may cause microexplosions in, for example, receptor cells. Damage may then occur as the result of displaced bulk. Vaporization may accompany the mechanical effects, resulting in the formation and collapse of large cavities, which are often seen as splits in the inner plexiform and nerve layers. Mechanical thresholds are inversely related to time, with thresholds lowest in the picosecond range. Lesions caused by mechanical insult are less homogeneous than thermal lesions, tending to follow the spatial distribution of the energy in the exposure.

Due to the nature of laser safety investigations, the use of human subjects poses serious methodological and ethical problems that are not easily resolved. As a consequence, intentional human laser exposure has been limited to those eyes that suffer severe retinopathies or eyes which are slated for early enucleation. The degradation of such eyes as well as the usual medical urgency for their removal prevents the performance of complete postexposure testing on these subjects (26, 27). Accidental laser exposures, on the other hand, are occurring more frequently and provide a means of investigating light effects. In these patients, however, it is often difficult or impossible to reconstruct the exact parameters surrounding the exposure and these patients are often unavailable for systematic follow-up investigations. As a consequence, most behavioral studies still must relied on suitable animal model for their investigations in spite of the obvious problems associated with species compatibility and behavioral training of nonhuman subjects to provide the index for the loss of visual sensitivity.

The selection of the rhesus as our animal model was based on the similarity of its retinal anatomy, physiology, and visual sensitivities compared to that of the human. Some discrepancies do exist in photoreceptor densities (28) and spectral transmission of light (29, 30) although morphologically the rhesus is quite similar to the human. Likewise, some differences exist in visual resolutions and spectral sensitivity between the two species although here again the differences are minor (19, 30, 31, 32, 33, 34, 35). The position of this species on the phylogenetic scale and its superior intellectual abilities, however, would lead one to assume that the strategies employed by these animals to com-

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pensate for any visual function may not be significantly different from those employed by their human counterparts.

The purpose of this project has been to delineate the immediate and long term effects that single and repetitive Nd/YAG pulses have on gross retinal morphology and visual functioning. We have examined small spot exposure effects over a wide range of exposure conditions that attempt to emulate field situations. Accidental exposures under these conditions may involve acute exposures well above the MPE and/or repetitive exposures at or below the MPE where chronic viewing might initially produce only transient effects on visual performance. Our experimental emphasis has relied primarily on analysis of functional losses immediately following laser retinal exposure, especially those changes in sensitivity that might pertain to applied military situations.

Although much work has been done in this area, there remains several issues still unresolved. First, the mechanism and cumulative nature that repetitive, lower-level (below ED_{50}) exposures have on visual sensitivity needs further delineation. Second, the strategies employed by exposed subjects to maintain visual vigilance need to be explored. This includes psychological factors such as shifts in motivations that might produce changes in self-imposed criteria used in decision making as well as changes in physical viewing strategies such as eye movements and central fixation. Third, the complexity of tasks used to assess visual functioning should increase to directly relate to real life situations. These factors require further evaluation not necessarily to reestablish standards so as to eliminate any possibility of damage (zero risk) but to establish training procedures and expectations of performance shifts for those situations where exposures might be likely.

METHODS

The method used to expose awake, task-oriented rhesus monkeys has been presented elsewhere (36) and will be only briefly discussed here. This method provides a reliable means of isolating punctate laser exposures onto specific regions of the retina without the use of anesthesia or other means of restraint. The method allows for the assessment of visual performance prior to, during, and immediately following laser exposures.

Subjects. Male rhesus monkeys ages 2 through 8 years and weighing 8 to 10 lbs were used as experimental subjects. No refractory errors or morphological abnormalities were observed in these animals' retinae and their pre-exposure visual acuities were within normal range for a variety of test conditions.

Subjects were housed individually in standard primate cages. During the entire course of the experiment they were free to move about in their home environment and were enriched with a variety of physical and psychological activities outside the laboratory paradigm. Enrichment activities included TV viewing, viewing self and other monkeys through mirrors, listening to audio tapes, solving food mazes, foraging for food and toys, rope climbing, manipulating wooden toys and sticks, and frequent interaction with animal caretakers and research personnel. Light/dark cycles as well as temperature and humidity were controlled. The animals' diets and liquid intakes were monitored and varied to produce a nutritious, yet enriching, experience. All animals were under veterinarian supervision. Each animal was routinely TB tested.

Apparatus. Prior to testing, each animal was fitted with a permanent light-weight, plastic neck collar which was used for capturing and securing the animal in the test apparatus. A portable restraint device was developed as a alternative to chronic chairing (37). This apparatus permitted easy removal and transport of animals from their home cage to the experimental chamber without the use of any form of anesthesia or excessive physical force. Restraint was necessary to maintain the animal's correct line of fixation and distance from the viewing screen. Proper positioning was an essential part of the methodology necessary for accurate measurements of visual acuity and for pre-determining placement of exposures on the retina. One of the major drawbacks to the use of nonhuman primates is that they can be very difficult and even dangerous to handle. This is especially true as the animal ages and when visual functioning is reduced due to laser exposure. Historically, when an experimental paradigm required even temporary restraint on a daily basis, chronic restraint devices such as primate chairs were employed. Since the experimental paradigm requires daily testing over an extended time period, this type of restraint was judged to be detrimental to both the welfare of

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the animal and the purpose of the experiment. On the other hand, daily administration of anesthesia was also judged to be undesirable since it might not only disrupt the experimental procedures, but also would be contraindicated medically.
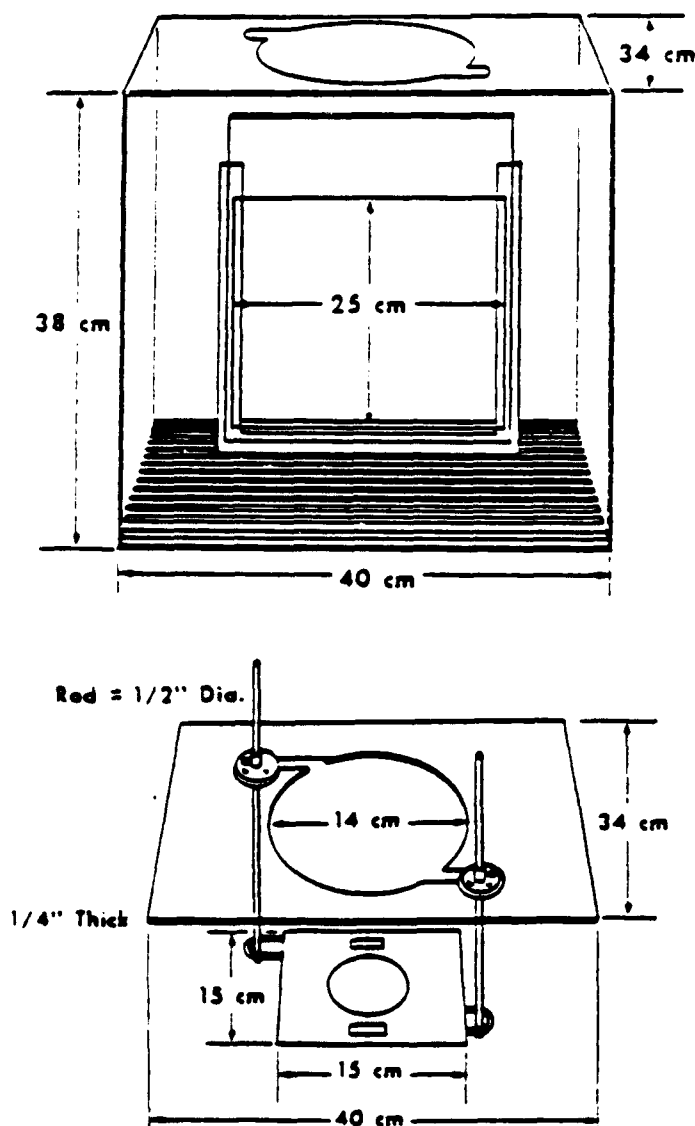

Figure 1. Diagram of the Plexiglas restraint device used during laser exposure and acuity testing. The overall dimensions of the cage as shown can readily accommodate animals of various sizes. A diagram of the collar, worn by the monkey, is shown in the lower diagram. Poles were used to withdrawal the animal's head through the hole in the top of the device and to secure the animal in position.

Our animals were conditioned to enter a specially designed squeeze device which easily

could be converted to a temporary restraint-type chair. The restraint device, which was mounted on the front of an animal's home cage, is shown in Figure 1. Initially, animals were conditioned to enter the device to receive a food reinforcer. Once inside the device, the animal's head was elevated with poles attached to the light-weight collar that was permanently worn by the animal. The restraint device was then moved into the test chamber and locked in position. Once inside the chamber, the animal was fitted with a customized Plexiglas helmet to minimized head movements. An opaque facemask with adjustable iris diaphragms was aligned with the animal's pupils so that eye position could be precisely established. Animals were positively reinforced with either fruit or juice for cooperative behavior.

Laser exposures and assessments of visual performance were made in the same light-tight, sound attenuated chamber. Both the experimental chamber and surrounding room housing the image and laser optical systems were painted black to minimize light scatter. A white noise generator was used to mask sounds generated by the experimental equipment. Mounted on the far wall of the experimental chamber was a rear projection screen subtending 3 deg at a distance of 1 m from the animal's pupil. Two carousel projectors, positioned outside the chamber, served as the source for image projection and the background of the viewing screen. Luminances and wavelengths of test targets and backgrounds were produced independently by neutral density and interference filters placed in the light paths. Both projectors were programmable and were internally able to optically read a variety of coded slides.

Acuity was measured using standard Landolt rings and gapless rings which were photographically produced on Kodak high contrast film (Kodalith). The rings were black on a clear background. The thickness of each Landolt ring and the width of the gap that formed the critical detail was always 1/5 of the diameter of that ring. The size of the gap could be varied from 0.25 to 30 min of visual angle in equal steps. The position and orientation of the gap in the Landolt rings was invariant. Except for the screen, the test chamber was entirely dark.

The presentation of slides, recording of the animal's responses, and reinforcements were all under computer control. A Cyborg ISAAC interface and Labsoft logic was used for

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programming purposes. All data was stored and analyzed on a standard IBM PC.

A second computer system was developed as a video image source. This system was capable of generating Landolt rings (rounded and squared) and computerized images that could be enhanced or degraded by varying the spatial frequency or contrast of the video image. This system also had the capacity of programming the presentation of computer-generated images and the accounting of responses generated.

Discrimination Task. Animals were trained using an avoidance paradigm to press a lever in the presence of a Landolt "C" and not to respond in the presence of gapless rings of equal dimensions. Failure of the animal to press the lever in the presence of a Landolt "C" (defined as "miss") or lever pressing in the presence of gapless rings (defined as a "false positive") resulted in the presentation of a discriminative tone and, on a variable reinforcement schedule, a brief, weak electrical shock. The negative reinforcer, produced by a high-tension coil, was annoying but not highly painful as the author can testify from experience. Swinnen, Brady & Powell (38) concluded that because of its short duration this type of shock is safer than conventional electric shock. Our animals demonstrated no reluctance to enter either the restraint cage or experimental chamber also indicating that the shock had no lasting psychological importance. The use of negative reinforcement was necessary in order to consistently maintain the animal's vigilance during the course of testing and especially immediately following laser exposure. A vigilant animal could avoid shock altogether.

Threshold acuity was derived using a modification of the von Bekesy tracking technique (39). In this technique, if the subject correctly detected the Landolt ring by pressing a lever (hit), a discriminable tone was presented and the next presented series of Landolt rings and gapless rings was 10-20% smaller. Incorrect detection of the Landolt ring (miss) resulted in a different discriminable tone, the possibility of a brief shock on either a fixed or variable ratio schedule, and the presentation of rings 10-20% larger. To discourage the animal from responding indiscriminately to all rings, a third discriminable tone was presented immediately following lever responses to gapless rings (false positive) and, on a fixed ratio schedule, the animal received a brief shock for these incorrect responses. The number of false positive responses was always low in trained animals (less than 10%). Using this paradigm, the size of the target was always at the animal's threshold thereby eliminating time which would have been spent testing targets either significantly above or below threshold. The targets were typically presented in sets of four rings that were of equal diameter. Three of the rings in each set were gapless, while the fourth was a Landolt "C" that appeared in a random position within the set. Each ring was projected for 2 sec. and there was a 1 sec. dark interval between successive rings. The size of the series was shifted only on responses to Landolt "C" rings and not to gapless rings. Baseline means, variability, and false positive responses in both the exposed and control eye were determined daily. All measurements were made under monocular conditions and after the animal had adapted to the luminance level of the screen.

Laser System. A Nd\YAG laser(Molectron MY 32-20) served as the exposure source. The 532 nm line was the primary wavelength used in this study; the invisible lines were blocked internally. The power densities of the beam were controlled by adjustments at the laser head and by neutral density filters placed in the beam pathway. Power densities were measured with a volume-absorbing calorimeter (Scientech, Model 363) and were expressed in uJ at the cornea. A small HeNe laser was used for aligning purposes and an Argon laser, mounted coaxial with the Nd/YAG laser, was used during portions of the chronic exposure paradigm. A diagram of the optical system is shown in Figure 2. The laser optical system produced a collimated beam of adjustable diameter from less than 50 microns to greater than 1,000 microns on the retina. Proper alignment of the laser beam with the animal's pupil and retina was critical. To align the beam, it was presented coaxial with a line between the artificial pupil and the gap in a specified threshold Landolt ring which subtended less than 1 minute of arc. For determinations of the line of sight, a 2 mm aperture was placed on the screen over the position of the gap in the specified Landolt ring. A mirror, approximately 2 m behind the 4 mm artificial pupil was then adjusted until it was normal to the line of sight. With the converging lens removed, the beam splitter at the junction of the image and laser beams was then aligned so that the collimated beam from the laser passed

through the 4 mm aperture and was reflected off the mirror back onto itself and through the 2 mm aperture at the projection screen. Coaxial alignments with the line-of-sight were then verified by noting that the reflected beam passed through both apertures and back on itself without any loss. The focusing lens was then positioned such that the cornea was in the focal plane of the lens and so as not to change the alignment of the beam with the line-of-adjustment. Presenting the beam in Maxwellian view reduced the possibility that changes in pupil diameter or small lateral movements of the animal's head would affect the amount of light entering the eye. The location of the exposure on the retina (on- or
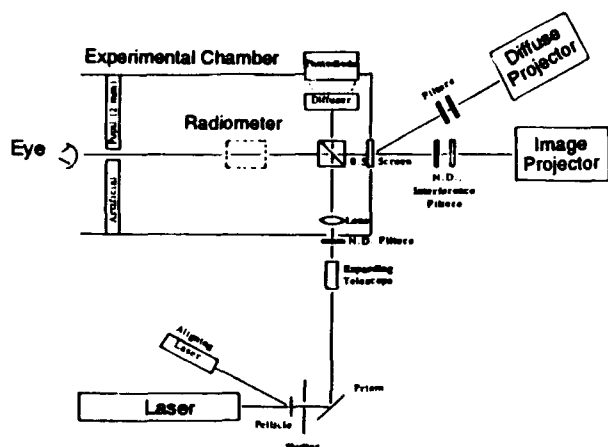

Figure 2. Diagram of the laser and image optical system. The laser beam was presented using a Maxwellian view and coaxial to the gap in a threshold Landolt ring. An CW Argon laser, not shown, could also be used for laser exposures and was positioned parallel to the Nd/YAG laser.

off-axis) could be varied by adjusting the position of the beam relative to the animal's point of fixation on the viewing screen.

Laser exposure. Prior to any laser exposure, stable acuity levels were established for each eye under a variety of different chromatic, luminance, and contrast conditions. Fifteen minutes prior to each exposure, acuity was again derived and failure of the animal to obtain a mean acuity within one standard deviation of his predetermined acuity level aborted the laser exposure. Session variability or an increased false positive response rate beyond a pre-established level also aborted the exposure session.

In cases where the animal did not achieve his pre-exposure baseline level in an eye which had previously been exposed, further exposures were discontinued and visual acuity testing was continued to establish the parameters of the visual deficit.

The laser flash was triggered immediately after the animal correctly detected a specified threshold Landolt. No exposures were made following incorrect detections of threshold targets or following correct detections during the final 1 sec of the trial. This procedure readily produced immediate and significant downward shifts in acuity were noted in over 80% of the exposures presented. In those cases where no such downward shifts in acuity were noted, it is possible that involuntary or pre-established voluntary eye movements may have lead to exposures in the peripheral regions of the retina. Given the nature of our acuity task, exposure of these regions of the retina would have been difficult or impossible to detect. Control or sham exposures with the laser beam blocked at the point of the safety shutter tested for any factors within the procedure which might change the animal's expectancy or response criterion.

Only one exposure session was scheduled per day except in those sessions where multiple pulses were indicated. At each power density, a repeated measures, random design was employed for each of the different types of exposure and viewing conditions employed. The order of laser power densities presented was fixed, beginning first with the lowest and increasing in a step-wise order following completion of all other conditions. Postexposure testing was terminated after the animal had regained his pre-exposure level for the given viewing condition or after 90 min of testing whichever came first. The animal's unexposed eye served as a control.

Statistical analyses of the data. Statistical comparisons were made of the changes in the degree and duration of the initial deficit as well as the total time for full recovery for the different exposure energies, durations, and spot sizes employed. Also examined was what impact the nature of the acuity task had on the magnitude and duration of the visual deficits.

The determination of the animal's performance level using the tracking technique was derived using the formula developed for the "Up and Down" procedure (40). Normally an animal's acuity was averaged for each running two minutes of testing before and after exposure.

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RESULTS

The ability of rhesus monkeys to resolve spatial targets of various luminances, contrasts, and wavelengths is remarkably similar to that of human subjects. This suggests the appropriateness of the rhesus as an animal model. Figure 3 demonstrates the comparison of rhesus and human visual acuity under a wide range of different luminance conditions. While slight differences can be observed at the extreme luminances, they can be explained by optical (pupil diameter) rather than physiological differences between the species. These differences do imply that the rhesus eye is a more efficient collector of light and this may affect damage thresholds. Foveal long wavelength insensitivity not shown here (19) also suggests that there is a difference in these two species in the distribution of long wavelength photopigments within the fovea which could affect the absorption of laser light restricted to this retinal zone. Similar comparisons of contrast sensitivity were also quite similar for the two species.
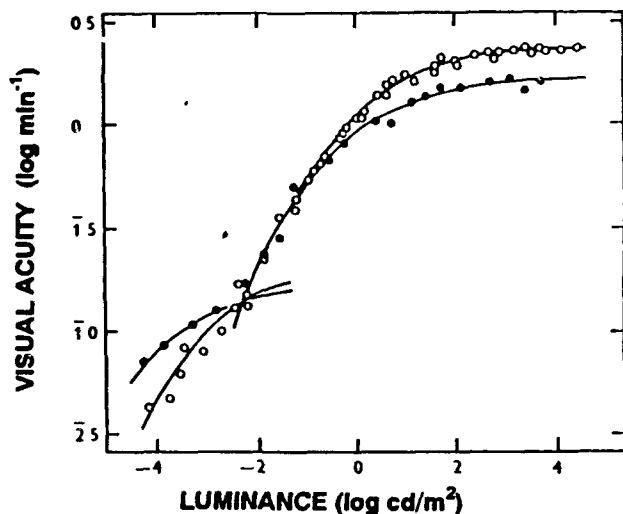

Figure 3. Comparison of rhesus (O) and human (O) visual acuity, measured with Landolt ring test objects. Mean acuities of 5 human and 5 rhesus were measured in the same apparatus. Background luminances of the different test targets varied over an 8 log unit range. The lines through the data were calculated using Hecht's 1939 photochemical equation. Under maximum photopic conditions, the acuity of human observers was about 17% higher than that of rhesus while under low luminance conditions, the rhesus performed as if they were receiving 4-5 times more light than the human observers.

FLASH EFFECTS. Visual acuity immediately prior to, during, and after laser exposure was measured using a tracking technique. Sample records of pre-exposure acuity and immediate postexposure acuity using this technique in an awake, task-oriented animal is shown in Figure 3. This figure also demonstrates the effectiveness of our procedure in producing an immediate deficit in visual performance following laser exposure.
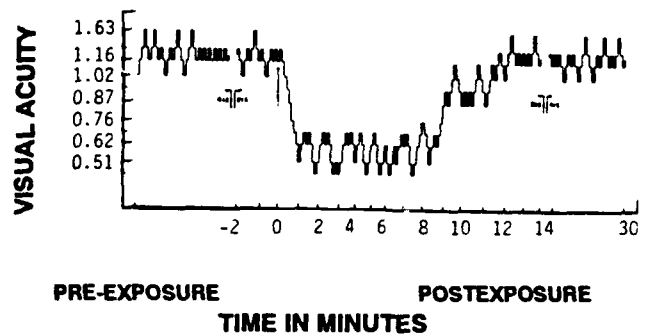

Figure 4. Sample raw data demonstrating pre-exposure acuity and the immediate drop in acuity following laser exposure. The occurrence of a single, 100 msec, 7mW, 632.8 nm foveal exposure is indicated in the figure by an arrow, and corresponds to the zero point on the abscissa. The ordinate indicates the various sizes of the gaps in presented Landolt rings and is plotted in reciprocal visual minutes of arc. This scale is measured in discrete steps, since the vertical excursions of the plot were taken from a non linear potentiometer mounted on the slide tray of a carousel which recorded tray position. The abscissa represents the presentation of the Landolt C's; corresponding times (in minutes) for representative trials are indicated relative to exposure.

Immediately preceding the exposure, the animal maintained a stable baseline threshold of 1.28 (min of arc)$^{-1}$. Immediately after exposure the animal's threshold decreased significantly (59%) and remained depressed for approximately 9 minutes before gradually returning to its pre-exposure level. Total recovery from the initial deficit was complete in approximately 13 min. No permanent shift in postexposure acuity was found at the energy level used in this figure.

Pre-exposure and postexposure measurements of visual acuity were assessed using a variety of wavelength and contrast conditions. Figure 5 demonstrates the effect that varying the viewing conditions had on deriving postexposure visual performance. In this example an animal was presented on three separate sessions iden-

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tical single 100 msec flashes that produced a 50 micron spot on the retina. This exposure produced only a temporary shift in acuity when tested with the three different contrast targets. For higher contrast targets, the initial percentage decrement in acuity was greater although recovery was quicker than for lower contrast targets. It should be noted, however, the baseline acuity achieved for both pre- and postexposure conditions significantly differed across contrast conditions. Under the high contrast conditions, acuity was higher and represented purely foveal activity while the acuity level achieved under low contrast conditions may have also represented parafoveal or even peripheral involvement.
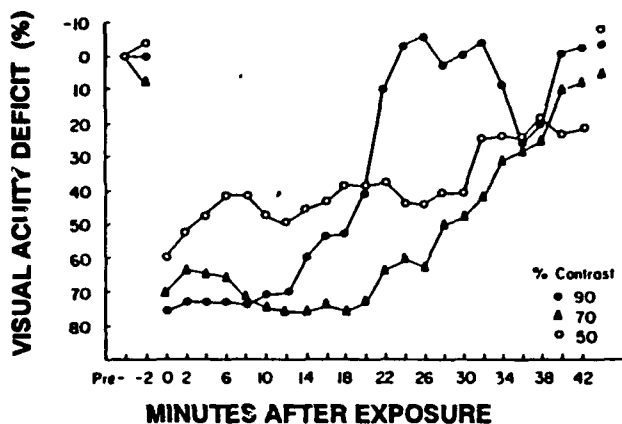
was significantly above the ED_{50} for this exposure condition and likely produced a small, ophthalmologically visible lesion. Due to its small retinal image size (<50 microns) and the brief exposure duration (15 nsec), the size of lesion produced would be extremely small and, as figure 6 demonstrates, only temporarily disabled this animal's foveal capability. Following exposure, the animal's visual acuity decreased by approximately 70% (to a Snellen acuity of 20/75) perhaps representing a dazzle effect and/or some transient disruption in the ocular media and photochemistry within the retina. Within minutes, however, the animal was able to compensate for this loss and acuity, at least temporarily, recovered to its pre-exposure level.

Figure 5. Effects of target contrast on postexposure performance. Exposures consisted of 2 mW, 100 msec flashes (514.5 nm) that produced a 50 micron spot on the retina. Only one exposure was made per session and the recovery functions shown represent the mean performance for several different exposure sessions. A random design of background contrasts (90, 70, 50%) was utilized. The background of the darkened Landolt ring was 640 nm. Other background wavelengths produced similar functions. For these exposure conditions, recovery was complete within the postexposure session and no significant long term deficit was noted.

Figure 6. Threshold acuity data following a single, 532 nm, 50 uJ pulse. The vertical lines through the data represent two minute time marks. Beam diameter on the retina represented less than 50 microns and was presented coaxial with a point on a visual target where the animal was required to maintain fixation.

In the previous two figures, exposure durations were relatively long (100 msec). With shorter duration exposures (15 nsec) of significantly higher energy densities, performance decrements were not necessarily more prolonged or greater in magnitude in spite of the greater overall power density per exposed area. Figure 6 shows the changes in an animal's visual acuity immediately following a foveal exposure to a single, 15 nsec pulse of 532 nm coherent light. The energy of this pulse, 50 uJ,

Although the visual deficit noted above appeared minor and transient, neither this animal nor others exposed under similar conditions appeared to be able to consistently maintain a stable baseline once the exposure had taken place. Typically prior to exposure, an animal's baseline acuity was remarkably consistent within and between sessions. Following exposure, however, these animals' baseline sensitivities generally decreased and their between session variability greatly increased in the exposed eye. Little or no differences were seen in the control eye. An example of the inability of an animal to maintain a consistent baseline acuity across sessions is shown in Figure 7. This animal's average daily postexposure acuity

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POSTEXPOSURE TESTING DAY

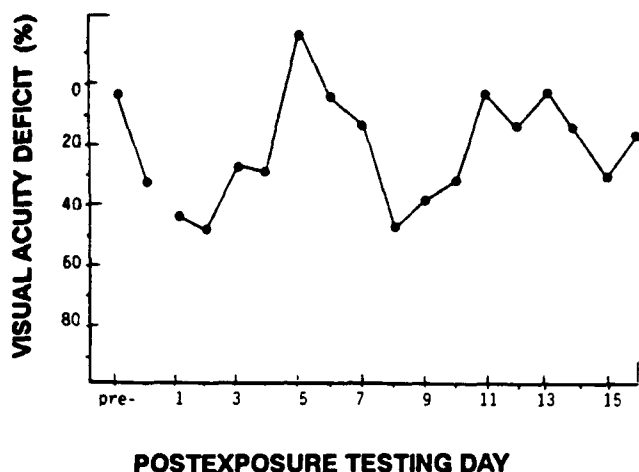**Figure 7. Daily mean postexposure acuity.** This subject was exposed to several 50 uJ, 532 nm pulses separated in time by several days. His last exposure data is shown in Figure 6. Each data point in this figure represents the average deficit over a 30-45 minute test session. No laser exposures were made during this testing period.

varied by as much as 50% from its pre-exposure level. No significant trends were observed over the postexposure testing period of several weeks and within session variability was not as markedly affected. These animals became increasingly agitated and uncooperative in spite of the positive rewards given during the test session.
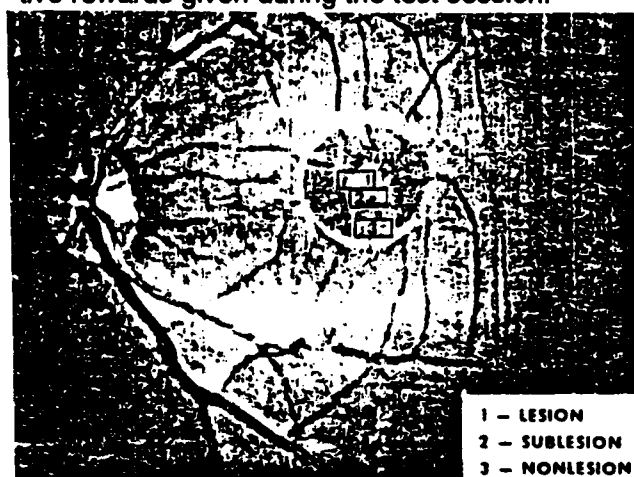

1 — LESION
2 — SUBLESION
3 — NONLESION

FIGURE 8a. Fundus photograph. This fundus photograph was taken almost immediately after the animal was exposed to single, 15 nsec pulses of 532 nm light. One exposure (marked #1) was significantly above the ED_{50} level for this exposure condition and the other (marked #2) was slight below the ED_{50}. A third region (marked #3) was used as the baseline measurement for the grey scale analysis.

The degree of morphological disruption produced by exposures of the type that elicit the behavioral changes shown above are presented in Figure 8. In conjunction with LAIR, fundus photographs of exposed retinae (a) were taken immediately after exposure and at selected intervals thereafter and grey scale analysis was then computed for different regions of the photographs. Single exposures at power densities above ED_{50} of relatively small retinal regions similar to those used in our behavioral studies produced only subtle pigmental changes. These changes could be accentuated by grey scale

1 = LESION
2 = SUBLESION
3 = NONLESION

1 = black, 64 = white
SHADES OF GREY

PIXEL LOCATION

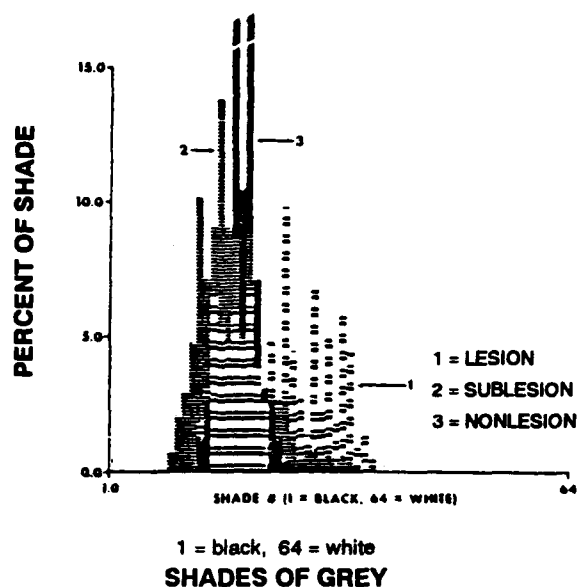**FIGURE 8b and c. Macular lesion grey scale distribution.** The distribution of reflectances for the lesioned lesioned macular zone is shown. The grey scale across different pixel locations (retinal regions) within the lesion is plotted to demonstrate the different reflectances at different zones (lesion, sublesion and nonlesion) within the affected area immediately after exposure and one hour postexposure.

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analysis (b) and compared over different retinal areas and times of assessment (c). The reflectance changes typically observed over an exposed region were first a reduction in reflectance followed within an hour by an increase in reflectance as indicated by the darkened then brightened grey scale analysis. When the exposures were intense enough to produce a hemorrhage, a clouding of the ocular media was observed which was observable in the grey scale analysis (d). In the behavioral study this corresponded in
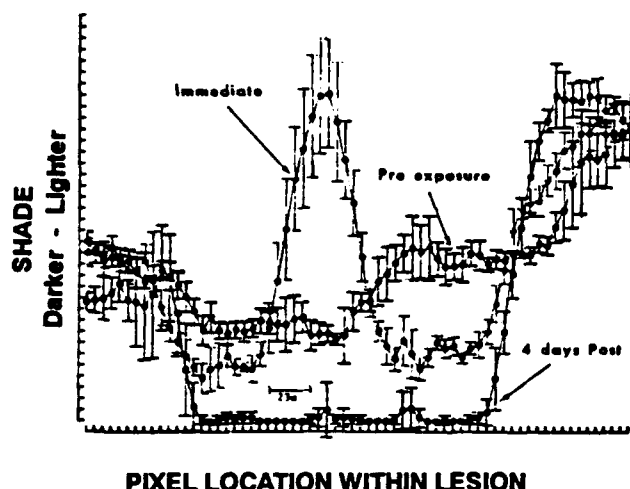
ple of this type of a cumulative effect is shown in Figure 9. In this example, recovery for each of the first three exposures was complete within 6, 10 and 18 minutes respectively. Recovery for the fourth exposure, presented several weeks after the initial exposure, was not complete within the test session. Without additional exposures, this animal's postexposure baseline sensitivity became more variant and daily postexposure acuity was similar to the example shown in Figure 7.

PIXEL LOCATION WITHIN LESION

Figure 8d. Grey scale analysis of Nd:YAG exposures at power densities well above the ED$_{50}$ that created a retinal hemorrhage. Similar to the grey scale analysis shown in portions 8a and 8c, the analysis for a second animal is shown. As a result of this exposure condition, the power density employed produced a retinal hemorrhage. Changes in the grey scale are plotted for different pixel locations before, immediately after, four days postexposure.

time to the observed decrement in visual acuity which improved considerably over the course of several days.

The behavioral deficits elicited by single, intense, Q-switched pulses presented to the same general retinal area often became more heightened for each consecutive exposure. This occurred in spite of the fact that each exposure was separated in time from the others by as much as several days. Typically, the initial exposure at a specific power density produced only a transient swift in acuity which completely recovered during the early portion of the postexposure testing. With each repeated exposure the time for fully recovery increased. An exam-

MINUTES AFTER EXPOSURE

Figure 9. Percent visual acuity deficit following repetitive, 50 uJ, 532 nm pulses. Recovery functions for four different 15 nsec pulses are presented. No more than one exposure was made per day and all exposures were presented coaxial to the gap in a threshold Landolt ring. Acuity was measured under maximum photopic conditions and plotted against the animal's pre-exposure baseline.
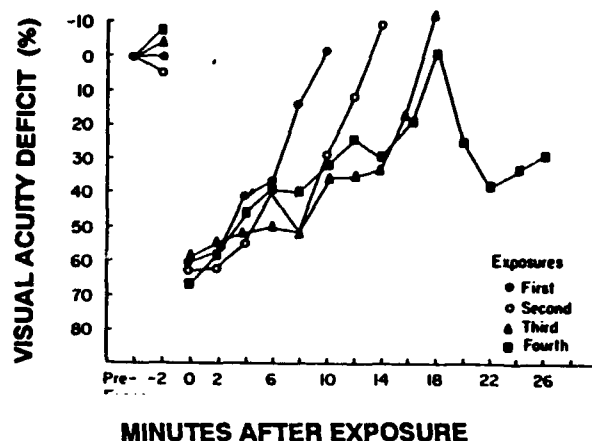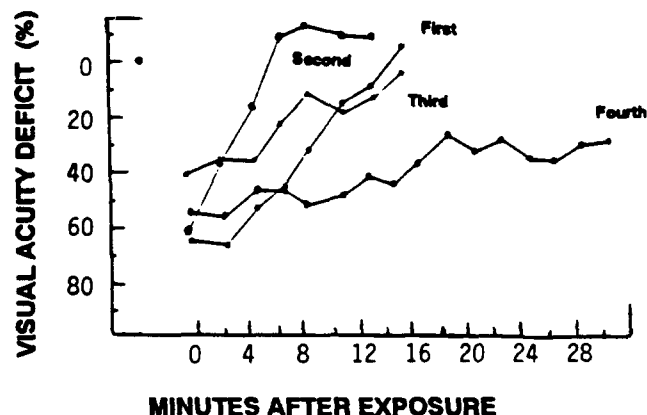

MINUTES AFTER EXPOSURE

Figure 10. Percent visual acuity deficit following repetitive, 100 uJ, 532 nm pulses. Recovery functions for four different 15 nsec pulses are presented. No more than one exposure was made per day and all exposures were presented coaxial to the gap in a threshold Landolt ring.

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A similar example for a second animal who was exposed to single pulses of equal energy over a period of several weeks is shown in Figure 10. In this case, like that shown previously, only one exposure was made per day but in this example the energy density of pulse was doubled that previously presented. While the initial behavioral deficits were similar to those shown in Figure 9 when plotted as a percentage of pre-exposure acuity, this animal's baseline acuity consistently dropped after each exposure and remained depressed during the several months while additional 100 uJ exposures were being made (Figure 11). In this figure the ordinate reflects the percent deficit from the animal's immediate baseline and not his original pre-exposure acuity prior to any exposures. His animal's baseline became progressively depressed following each exposure session. Initial recovery to the animal's daily baseline was complete within 15 minutes of the exposure for the first three laser pulses and the observed deficit, although initially slight, was not evident until several days later. Following the fourth,

become significantly reduced and remained so for several months.

In order to further delineate the extent of the deficits elicited by consecutive exposures of the nature described above, targets of various contrasts were superimposed on different wavelength backgrounds. In Figures 12 and 13, baseline acuities over a period of 4 weeks following laser exposure were obtained for these different viewing conditions. In the examples provided, the animal had previously been exposed to a series of single 50 uJ pulses which eventually led to a permanent visual deficit. This animal's pre-exposure acuity to Landolt rings of various contrasts is shown in Figure 12. Peak acuity was observed when intermediate contrast targets were used. Acuity to high contrast targets (97%) was slightly less and acuity dropped off sharply as the contrast decreased below 80%. Two weeks after the series of relatively intense laser exposures, this animal demonstrated no differential sensitivity to targets varying in contrast between 60% and 98%. For all
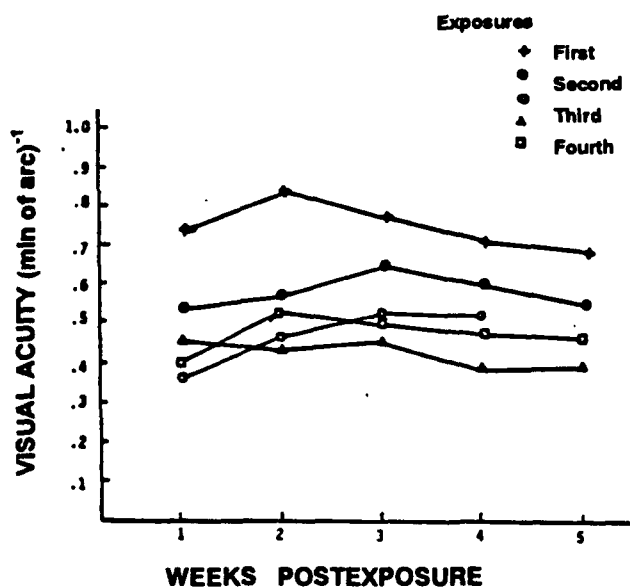

FIGURE 11. Mean acuity levels following four, separate 100 uJ pulses. Each of these curves represent the average daily acuity for the time periods indicated. Visual acuity was derived when maximum photopic conditions using achromatic targets. No laser exposures were made during the time these measurements were being made.

CONTRAST (PERCENT)
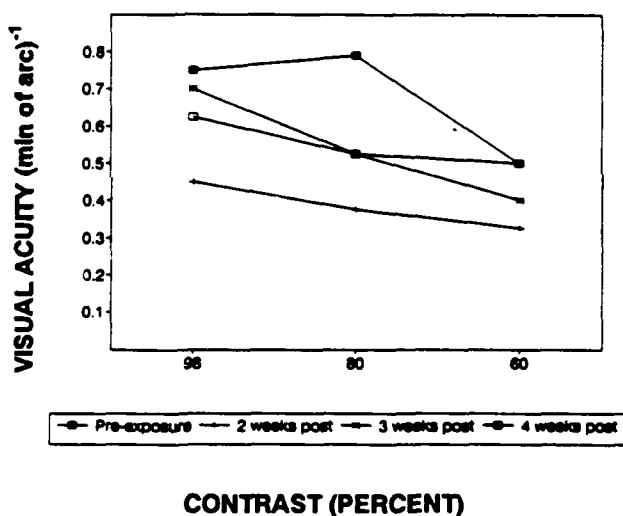
Figure 12. Postexposure acuity to various contrast targets. This animal was exposed to a series of 50 uJ, 15 nsec pulses from a Nd/YAG (532 nm) laser. Postexposure acuity for each contrast target was measured over a period of four weeks. Each data point was derived from 10-15 minutes of daily postexposure testing during the weekly period indicated.

and final exposure, a new depressed baseline was immediately evident during the test session and by this time the animal's overall acuity had

contrast levels shown, the animal's acuity was significantly depressed from his pre-exposure level. No differential contrast sensitivity was noted. Within four weeks of the last exposure, this animal's visual acuity had increased signifi-

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cantly across the range of contrast targets employed, although no selective enhancement comparable to the pre-exposure condition was observed for intermediate contrast target.

Postexposure acuity was also measured under various background wavelength conditions; all equated for equal numbers of quanta. The subject tested and the postexposure time period shown here is the same as that shown in Figure 12 for contrast sensitivity. During pre-exposure testing this animal demonstrated a maximum visual acuity when the darkened rings were presented against mid-wavelength (540 nm) backgrounds although the animal maintained a elevated acuity also to targets against a long wavelength (620 nm) backgrounds. This animal performed significantly poorer when the background was shifted towards the short wavelength region (480 nm) of the visible spectrum. Other wavelengths were tested but, for clarity, not included in this figure. Following exposure, acuity was somewhat uniformly depressed across the entire visible spectrum and remained depressed for several weeks before partial recovery was evident. Recovery was greatest in the intermediate region (540 nm) and least in the short wavelength region. After several months, the animal's spectral acuity still
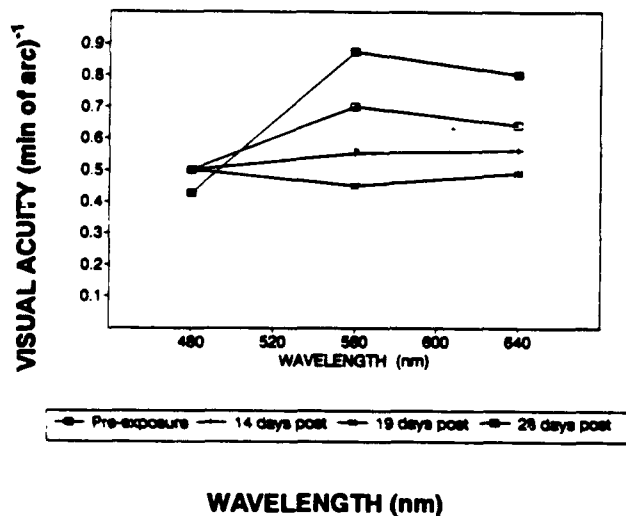
had not returned to its pre-exposure level in spite of the fact that there were no comparable shifts in the animal's control eye or in acuity derived for achromatic targets.

For exposures that were relatively short in duration and which were also spatially restricted (<50 microns on the retina), recovery was always quite rapid. Slight variations in exposure durations had only a minimal effect on recovery time. With longer duration exposures, however, even relatively small laser spots required a significant time for full recovery. Figure 14 shows the recovery functions for four different exposure durations ranging from less than 20 msec to greater than 100 msec. These exposures were relatively low in power density and were not intense enough to produce a permanent change in the animal's postexposure acuity.

WAVELENGTH (nm)

Figure 13. Spectral acuity following repetitive 15 msec pulses of 50 uJ Nd/YAG light. This animal was exposed in a manner previously described to four, 50 uJ pulses of 532 nm light that produced a minimal spot (<50 microns) on the retina. The separate exposures were presented over a period of several weeks. Darkened rings were presented against different chromatic backgrounds which were equated for equal numbers of quanta. Each data point represents the mean acuity of a minimum of twenty minutes of threshold acuity measurements.

MINUTES POSTEXPOSURE

Figure 14. Effects of exposure duration on postexposure visual acuity using minimal diameter (50 micron) Argon (514.5 nm) flashes. Individual recovery functions were derived for one animal exposed repeatedly over several different exposure sessions. Visual acuity was measured using an achromatic, high contrast background. Each data point represents the means of several different exposures.

Reminiscent to Figure 6, when relatively brief flashes were made that irradiated very small regions of the retina, visual recovery is almost immediate (within 4 to 6 minutes). When the exposure duration was increased to greater than 100 msec as shown here or when repetitive, brief exposures were made within a single exposure session, eye movements acted to

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spread the irradiation over larger and larger retinal regions. The involvement of larger central zones significantly increased the time it took for recovery.

Figure 15 demonstrates that recovery time remains very rapid even when relatively intense exposures are made. The exposures, however, must be relatively small in diameter (<100 microns), presented for only brief periods (<50 msec), and their overall power densities must be below the point of producing optical clouding. In this figure, the exposure duration of the single, 50 micron spot was 15 nsec. The raw data shown reflects little change in the ability of the animal to detect the gap in threshold Landolt rings in spite of the fact that the power density of the exposure was significantly greater than other exposures that produced deficits that took a long term to recover. Apparently the nature of the visual task allowed animals exposed in this

shifting their fixation to new, unaffected regions of the fovea. In Figure 15 no immediate shift in the animal's tracking performance can be noted in spite of the fact that the testing conditions were similar to those shown in Figure 4 where a significant drop in acuity was clearly evident immediately after exposure to a much less intense flash. The difference between the two exposure conditions was primarily the area of involvement. A slight, though statistically insignificant, gradual downward shift in the animal's postexposure baseline can be noted in Figure 15 as the postexposure testing period continued.

TIME (Days)
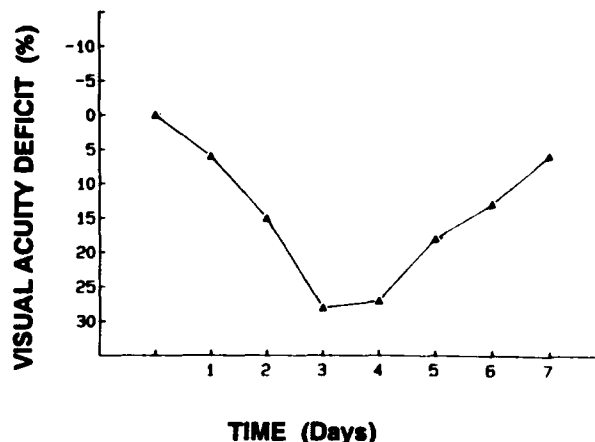
FIGURE 16. Average session acuity over a one week period following exposure. Visual acuity was derived for each of seven days following a single, 100 uJ, 532 nm pulse. Mean acuity was derived using the up and down method and the session variability did not significantly vary from day to day or from the animal's pre-exposure level. Also, no significant shifts in the animal's control eye were noted over this same time period.
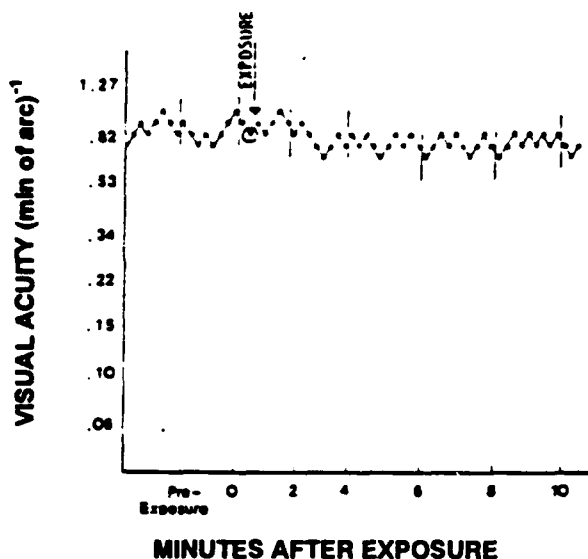

MINUTES AFTER EXPOSURE

FIGURE 15. Sample tracking data prior to and immediately following a single, 15 nsec, 10 uJ pulse. Beam diameter of the spot presented coaxial with the gap in a threshold Landolt ring was less than 50 microns on the retina. The 532 nm pulse was slightly above the projected ED$_{50}$ level for this exposure condition. The vertical lines through the data represent 2 minute time intervals. Each filled circle represents the presentation of a Landolt ring and the vertical lines between the circles represent the presentation of gapless rings of the same diameter. The size of the test targets are indicated on the ordinate. Each target was presented for 2 sec and the size of the next series of test targets was contingent upon the animal's correct detection of the Landolt ring within the series of gapless rings.

manner to quickly compensate for their losses by

Daily exposure to a 10 uJ pulse ultimately did increase the magnitude of the initial reaction to the exposure but did not produce any significant permanent shift in acuity when only achromatic test targets were employed.

In some situations what appeared to be only a minor shift in postexposure acuity immediately following the exposure increased in severity over a period of several days. Figure 16 demonstrates a case where an animal appeared to have only a minor shift in postexposure acuity during the exposure session (similar to that shown in Figure 15) and where full recovery seemed evident by the end of the exposure session. However, in the days thereafter this

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animal appeared unable to establish his pre-exposure baseline in spite of the fact that no further exposures were made. In this example, the visual deficit increased significantly over the next three days before gradually returning to his pre-established level nearly a week later. The data points in this figure represent the mean acuity for the test session and within session variability did not significantly vary from the animal's pre-exposure level. Hence, this effect was dissimilar from that noted in Figure 7 where postexposure acuity was also affected but because of within and between session variability, no systematic trend for the deficit or recovery could be established for that exposure condition. The nature of the delayed effect shown in this figure may have been the result of ocular clouding due to bleeding rather than due to pigmental or neural changes which, in the case shown in Figure 7, might have led to a less stable and systematic result.

Since the consequence of any laser exposure, in part, is a function size of the area involved, we have explored the impact that changes in retinal spot size have on the magnitude and duration of the elicited deficit. Using a 15 nsec pulse virtually eliminated any effect that
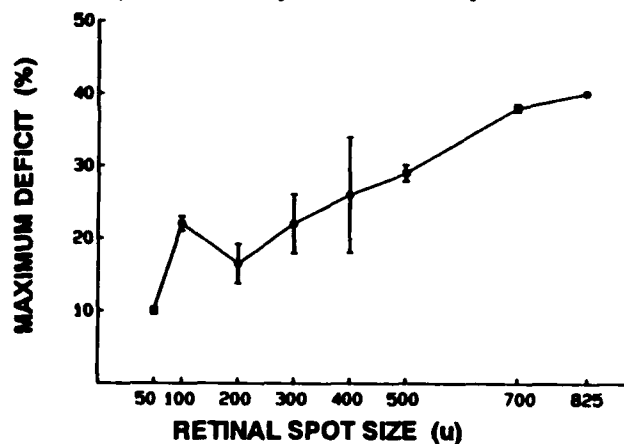

Figure 17. Effects of spot size on the magnitude of the initial deficit. This subject was exposed daily to a single, 3 uJ pulse from a Nd/YAG laser. Each exposure was presented on-axis while the animal was attempting to detect a threshold Landolt ring. Acuity was measured using a high contrast, achromatic target. Each data point represents the mean deficit of several different exposure sessions and the vertical bars represents ± 1 SD.

either voluntary or involuntary eye movements might have on the size of the retinal irradiation. The impact that varying retinal spot sizes from

50 to 825 microns had on the magnitude of the initial deficit is shown in Figure 17 and 18 for two different animals. In Figure 17, for relatively small diameter exposures the magnitude of the initial deficit was approximately 10% while for relatively large diameter exposures this deficit increased to approximately 40%. Between these two extremes, an almost monotonic function was noted for this effect. Only one exposure was made per day and at the energy levels employed, no cumulative or long term deficit was produced. In Figure 18 a family of curves are presented for five different power densities and six different spot sizes. As previously shown, the initial deficit varied from less than 10% when relatively small spot sizes were used to greater than 40% for the largest spot sizes. Variations in exposure density over a greater than 10 fold range produced little impact on the size of the visual deficit although did significantly alter the time for full recovery from the deficit especially for those situations where large diameter exposures were employed.

Unlike the size of deficit being dependent upon spot size, the time required for full recovery from exposures of the type described above appeared independent of the beam diameter (see Figure 19) as long as the energy densities of the exposures were invariant. For relatively large diameter exposures we have previously demonstrated that recovery time is monotonically related to the energy density of the exposure. For Q-switch pulses, the total recovery time was really quite rapid and the diameter of the pulse on the retina was less a factor in predicting this time than other physical parameters of the pulse.

The exposure parameter that appeared to be the best predictor of recovery time was power density. The greater the power density typically the more prolonged the recovery time. Partially confounding this prediction when using extremely short duration exposures (15 nsec), however, was spot size. With longer duration exposures or with multiple pulses, the area of involvement became less crucial in deriving recovery time. Figure 20 shows the relationship of power density to recovery time for exposures that also varied in spot size. For the lowest power densities shown, recovery time was also dependent upon the size of the retinal exposure; the larger the area, typically the longer it took for the animal to fully recovery from the flash. On the other hand, for the highest power density shown, the size of retinal involvement had less of an effect. While considerable inversions can
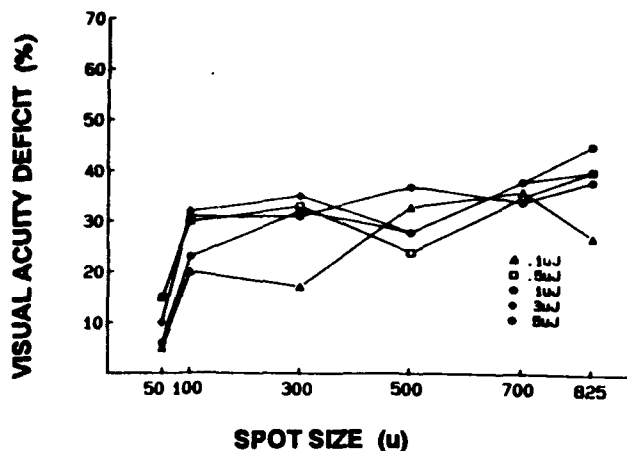
15

FIGURE 18. Size of the elicited deficit for various beam diameters and energy densities. This subject was exposed daily to single, 532 nm pulses. Each exposure was presented on-axis while the animal was attempting to detect a threshold Landolt ring. For each spot size, the energy of the exposure ranged from 0.1 uJ to 5uJ. A random design of exposure diameters and energies was employed. Acuity was measured using a high contrast, achromatic target and under these conditions no permanent deficit was noted.
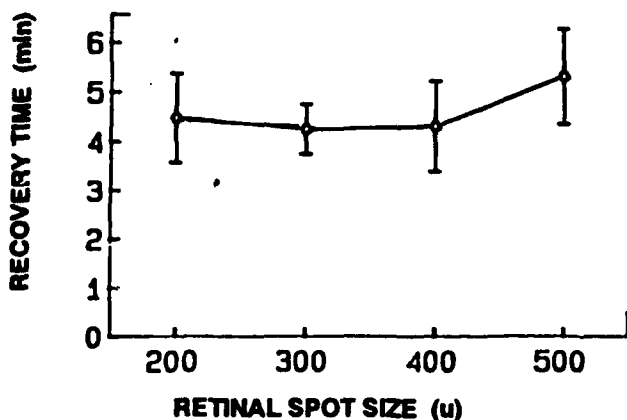

Figure 19. Effects of spot size on recovery time. This subject was exposed daily to single, 3 uJ pulses from a Nd/YAG laser. The exposure was presented on-axis. Acuity was measured using a high contrast, achromatic target. Each data point represents the mean time for the animal to regain his pre-exposure acuity and the vertical bars represents ± 1 SD over several different exposures for each size image.

be noted for intermediate power densities, this figure demonstrates that generally recovery time increased as the power density of the exposure increased regardless of spot size. Thus, exposure energy primarily affects recovery time while exposure spot size primarily affects the magni-

tude of the deficit so long as other exposure conditions are consistent. The larger the retinal area involved the more consistent the relationship between power density and recovery time became. The same was true for spot size versus the magnitude of the deficit. The longer the exposure duration the more consistent this relationship became.

POWER LEVEL (uJ)
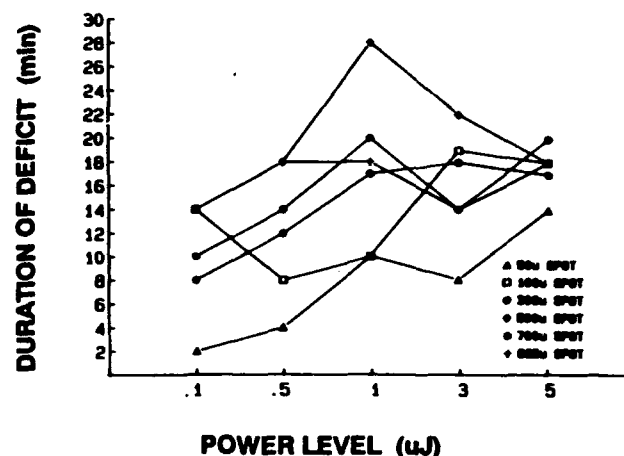
Figure 20. Length of visual deficit for various power densities and spot sizes. The mean recovery times are shown for one animal exposed to a series of 15 nsec, 532 nm pulses that were varied in power density and spot size. Only one exposure was made per session and recovery time was defined as the first two-minute interval that the animal maintained an acuity level comparable to his pre-exposure baseline.

MULTIPLE PULSES. Multiple exposures presented within a single session were employed to increase the area of retinal involvement and to test for any cumulative effects that this type of exposure condition might produce. Typically the pulses were presented in rapid succession of each other and within a 100 msec window to eliminate any unpredictable effects that involuntary eye movements might produce. The number of pulses employed varied from one to four. Figures 21 and 22 compare the impact that single versus double exposures have on the total time for full recovery (Figure 21) and size of the initial deficit (Figure 22). This comparison was made for six different diameter exposures in the same subject. Only one exposure condition was tested per day. For each condition, the double pulse was more

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effective (i.e. produced a larger initial deficit and longer recovery time) although the differences were not dramatic. As previously shown, Figure 21 demonstrates the independence of spot size on the duration for recovery. The double vs single exposure condition generally increased the recovery time by approximately four minutes while increasing the magnitude of the maximum

FIGURE 21. Recovery time for different diameter exposures presented as either a single pulse or double pulse. The total time for full recovery following either a single or double 15 nsec pulse(s) is plotted for different diameter spot sizes.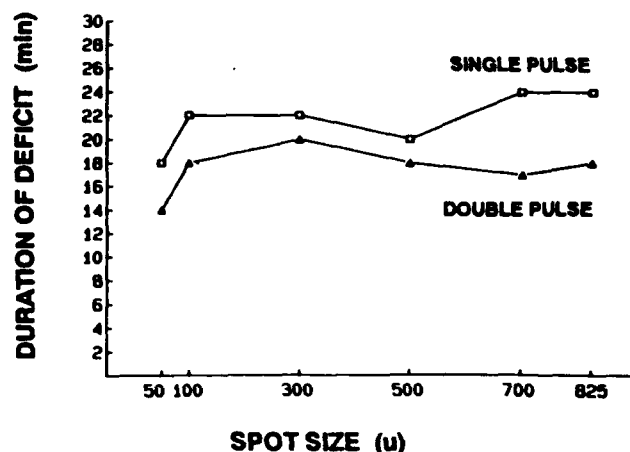 In each case only one exposure condition was presented daily and full recovery was complete from each exposure within the test session.

FIGURE 22. Magnitude of the initial visual loss for different diameter exposures presented as either a single pulse or double pulse. The magnitude of the initial deficit following either a single or double 15 nsec pulse(s) is plotted for different diameter spot sizes. In each case only one exposure condition was presented daily and full recovery was complete from each exposure within the test session.
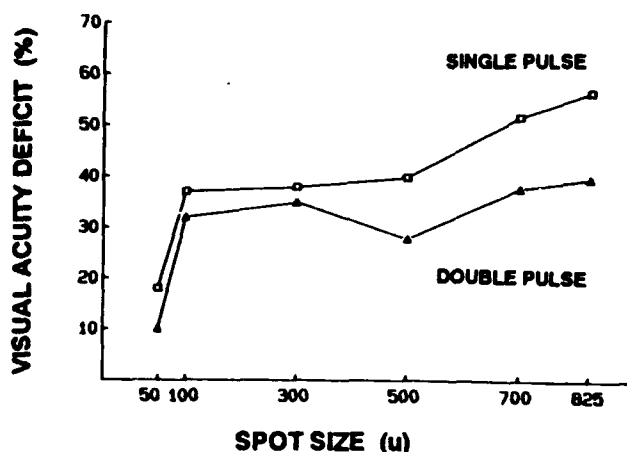
deficit by approximately 10% across all spot diameters. Similar enhancement of visual deficits were noted in other animals when the number of pulses were increased.

The effectiveness of the exposure in producing a long term deficit was increased by the presentation of multiple pulses within a 100 msec window. In Figure 23 is presented the recovery periods for different numbers of exposures at various power densities. Recovery functions for one, two, three, or four pulses presented successively are shown in this figure. For the single pulse condition, the recovery period was quite rapid even as the power density of the pulse increased. Exposing the animal to additional pulses generally increase the time required for recovery by as much as 10 fold. The increase was particularly obvious for intermediate power densities.
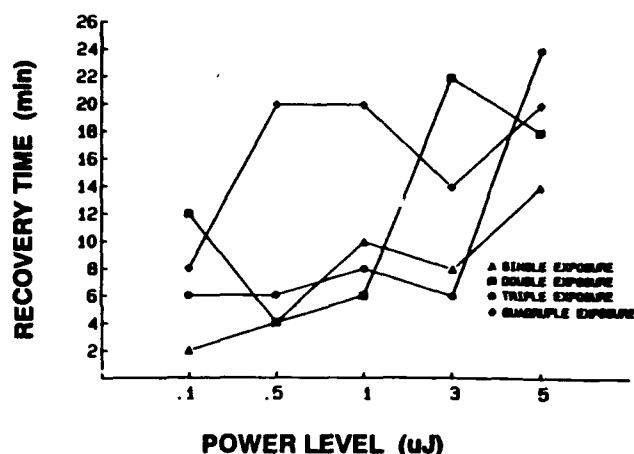
Figure 23. Length of visual deficit for different power densities and number of pulses. Each curve is represents the time required for the animal to re-establish his pre-exposure baseline immediately following laser exposure. Each exposure consisted of either a single or multiple pulses of 532 nm light presented coaxial with the gap in a threshold Landolt ring. Each pulse produced a 50 micron spot on the retina and when multiple pulses were present, they were all presented within a 100 msec time period.

In the previous examples where multiple pulses were presented within the same session, no attempt was made to control for cumulative impact of the energy densities. Indeed, one could argue that the greater visual deficits and longer recovery times noted above could simply be due to a doubling of the energy of exposure. The confounding effect of differential energies

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of differential energies was eliminated in a series of exposures in two animal where the energies of individual pulses were equated for the number of pulses presented within the session. The exposure paradigm was essentially similar to those previously discussed. All exposures were presented as closely in time as physically possible and within a 100 msec window of each other. The total power density of the exposure session was 3 uJ; presented
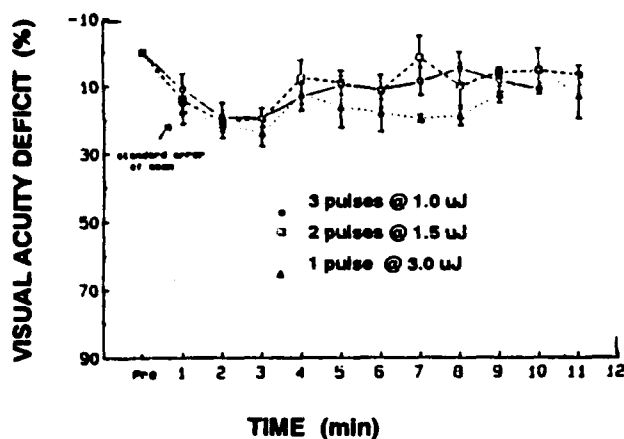
FIGURE 24. Effects of single vs multiple pulses equated for total energy. The total energy density of the 532 nm exposure was 3 uJ and was presented either as a single, 15 nsec pulse or as two or three pulses all presented within 100 msec of each other. Only one exposure condition was run per session and the animal's visual acuity was followed for a period of 30 - 45 minutes postexposure. An average of five different exposures were made for each condition shown. The vertical bars about each data point represent the standard error at each of the running minutes indicated.

either as a single pulse, two 1.5 uJ pulses, or three 1 uJ pulses. In this condition, like in others where the exposure area was relatively small due to the brevity of the Q-switched pulses (15 nsec) and the restricted nature of the beam (<50 microns), the elicited visual deficit was rather small. As seen in Figure 24, maximum deficit did not exceed 20% of the baseline level. These deficits likewise lasted only several minutes before either partially or fully recovering. Recovery was typically complete within 10-15 minutes. While the time course of the recovery varied somewhat across conditions, no significant difference was noted for single, double, or triple pulses equated for total energy. Following some exposures the animal had difficulty re-establishing his baseline level but in no case

were visual deficits observed 24 hours after the exposure.

A composite of the impact of single vs multiple pulses equated for total energy is presented in the next two figures. This data is the average of 5-7 exposures presented over a period of several weeks. When averaged and presented in this manner, mean recovery time appeared slightly longer for the single pulse condition for both animals although the overall differences were not great. Likewise, a very slight trend of a somewhat larger maximum deficit was also noted for the single exposure condition but the effect here was much less.

NUMBER OF PULSES
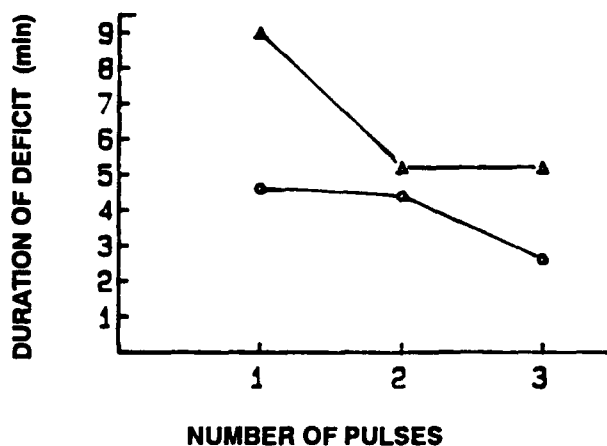
FIGURE 25. Impact of single vs multiple pulses equated for total energy on the recovery time The two curves represent that average data from two different animals. Each data point represents the mean of 5-7 exposure sessions presented over several different weeks. Only one exposure condition was presented per session and postexposure testing was continued until the animal re-established his baseline acuity level. These animals were exposed to either one, two, or three 15 nsec pulses. The total energy density per exposure was 3 uJ. The 532 nm, 50 spot exposure was presented on-axis. Acuity was measured using high contrast, achromatic targets.

GLARE EFFECTS. Exposure to lasers may not be restricted solely to the acute situation. While acute exposure conditions are more likely to lead to adverse morphological changes within the retina they may not produce as significant a performance alteration as chronic exposures to relatively low energy laser light. The acute exposure situation is characterized by rather intense energy densities restricted to isolated, though often functionally sensitive,

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regions within the retina mosiac. As previously demonstrated, these types of exposures produce an immediate decline in visual acuity in the range of 20-40% that, depending upon the energy of the flash, may last several minutes to several months. Because of the short duration of these exposures (nanoseconds) and the few number of pulses produced, the areas of retinal involvement would be quite small. Individuals experiencing this type of exposure should be able to "look around" the altered area and, if sufficiently motivated, use unexposed portions of their retina to complete visually guided assignments.
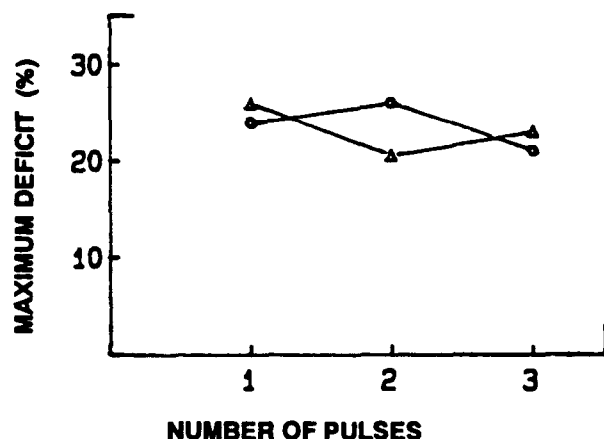

FIGURE 26. Impact of single vs multiple pulses equated for total energy on the size of the initial deficit. The two curves represent the same exposure conditions and animals described in Figure 25. Instead of computing recovery duration, this figure examines the magnitude of the acuity deficit immediately following exposure. The deficit is plotted in terms of percent deficit from the animals' pre-exposure levels. These exposures produced no long term deficit.

In this portion of the report we have examined what impact chronic laser viewing might have on on-going visually guided behavior and on the long term functioning (sensitivity) of the visual system. The exposure parameters that characterize this type of condition are generally not spatially restrictive in nature. The energy densities associated with chronic viewing of laser screens are considerably lower and presumably well below the interpolated ED_{50} for this exposure condition. In our paradigm the exposure spot size was increased significantly from the minimal diameters (<50 microns) used previously in the acute studies. Extending the

duration of the exposure also amounted to extending the area of involvement since the animal's involuntary and voluntary eye movements likely extended the exposure over even larger areas than would have otherwise occurred. We chose to use the same optical pathway as used in our acute studies and to place the extended beam either in the center of the discriminanda (termed on-axis) or slightly displaced horizontally from this point (termed off-axis). In the on-axis exposure condition, the animal was forced to "look through" the laser irradiation to made the required discrimination since the laser remained on during the time the stimulus was presented and it totally covered the critical feature of the discriminanda. Regardless of where the animal positioned its eye, the laser irradiation was present, covered the full extent of discriminanda, and produced a glare effect. If the animal "looked away" from the laser spot, the critical feature of the discriminanda would now fall on peripheral regions of the fovea where visual acuity would be greatly reduced. If the animal maintained foveal fixation on the target as he had been previously rewarded for, significant bleaching of the foveal pigments would likely occur thereby also reducing the visual resolution capacity of this sensitive region.

Chronic exposures varied in power density, duration, spot size, and position, relative to the discriminanda, on the retina. Position of the laser spot was established by locating the beam either coaxial with the gap in a threshold Landolt ring (the discriminanda) or displacing it several degrees horizontally from the gap. Exposures were produced either by a series of 532 nm pulse trains from a Nd/YAG laser or by an Argon laser. The perceptual consequence of this type of exposure was an almost constant laser spot superimposed on the viewing screen. Exposure durations were timed through a conventional electronic shutter placed within the optical pathway.

Initially, the overall duration of the pulse trains were relatively short, lasting only several seconds or minutes. The size of the beam was expanded to produce as large a diverging spot as possible. Our primary concern at this point centered on the time required for full recovery once the exposure terminated and not the level of performance during the exposure. Figure 27 demonstrates the typical recovery noted following the termination of the exposure. These recovery functions were similar to those observed for the single pulse condition. For all
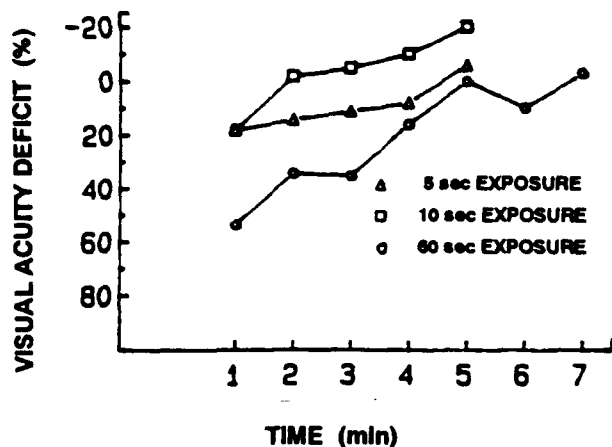
Figure 27. Visual acuity following prolonged exposure to 532 nm light. The duration of the pulse train varied from 5 to 60 seconds and the power density was 2 uJ. The diverging beam created a 1000 micron spot on the retina and was presented coaxial with the position of gaps in Landolt rings. When viewed on the screen, the laser spot completely filled the area occupied by the discriminanda and partially covered the remainder of the figure. Only one exposure condition was presented per session and postexposure testing continued until the animal's acuity returned to its pre-exposure level. The deficit noted was derived from the animal's pre-exposure level and not the acuity level maintained during the exposure itself.

three exposure durations full recovery was complete within 7 minutes of the termination of the exposure. The nature of these functions are reminiscent of those presented for the single pulse condition although for the exposure condition shown in this figure, recovery was somewhat more rapid. The animals were able to maintain a stable, although depressed, acuity level during the exposure. Due to the relatively short duration of the exposure, an accurate measurement of acuity could not easily be established while the laser was on. The magnitude of the visual deficit immediately following the exposure, however, typically was larger than those noted previously when on a single pulse was presented. This larger deficit was likely due to the larger overall area of retinal involvement ard the inability of the animal to be able to "look around" the irradiated area during the exposure. Recovery time was longest and the magnitude of the deficit greatest for the longest duration exposure although the differences, especially in total recovery time, were not significantly different across the durations shown here. For the shortest duration exposure, recovery was

remarkably quick and no long term changes were noted for any of the exposure conditions presented.

Exposure to more prolonged laser light produced serious disruptions in the ability of the animal's ability to resolve the target while the exposure was taking place. During on-axis exposures, the visual targets typically had to be increased to the point that they almost filled the entire viewing screen. While being exposed animals appeared to maintain their vigil, responding only to the largest of targets and not significantly varying their false positive rate to gapless rings.

As previously shown with single or repetitive pulses the nature of the visual task directly affects the nature of the performance deficits observed. This was also the case in the chronic exposure condition. Using different energy densities and exposure positions (on- and off-axis) we have explored what impact variations in target contrast and background wavelengths have on the ability of the animal to maintain a baseline acuity during and immediately following laser exposure. A series of representative curves for high (90%) and intermediate (60%)
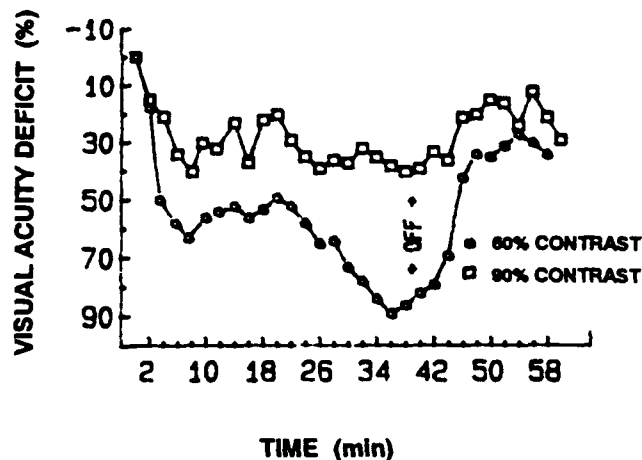
Figure 28. Effects of target contrast on visual performance during and immediately following prolonged exposure to 532 nm laser light. A sustained train of pulses covering the entire visual field of the discriminanda was presented for 40 minutes. The overall power density of the pulses was 0.01 uJ and their beam diameters exceeded 1000 microns on the retina. The time marker indicates the onset of the exposure and its termination at 40 minutes is marked within the figure. Visual acuity was derived using two different contrast targets. The two functions represent two different exposure sessions presented several days apart.

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contrast targets are shown in Figure 28. In this figure two exposures that were much less intense, but more prolonged in duration are presented. The train of pulses used was superimposed onto the area where the discriminanda was located (on-axis) and the exposure lasted for 46 minutes. The animal maintained its visual task during the exposure and visual acuity was derived for each running two minutes during and after exposure. The energy of exposure was relatively low (.01 uJ) but, because of its prolonged duration, produced a rather substantial and sustained deficit. The observed deficit was greatest for the low contrast viewing conditions. For the high contrast condition, acuity dropped approximately 30% from its pre-exposure level and the animal was able to maintain this level of performance during the 40 minute exposure. Following the termination of the exposure, acuity first began to recover, then returned to its depressed level during the next 15 minutes. Since the animal had been tested for over one hour, after 15 minutes of postexposure testing the animal was given a rest period. Following the brief respite the animal's performance returned to its pre-exposure level and remained at this level for the next several days. When tested

under low contrast conditions, the size of the deficit was greatly enhanced. Initially, the animal's acuity dropped to approximately 50% of its pre-exposure level and remained depressed at this level or lower for the durat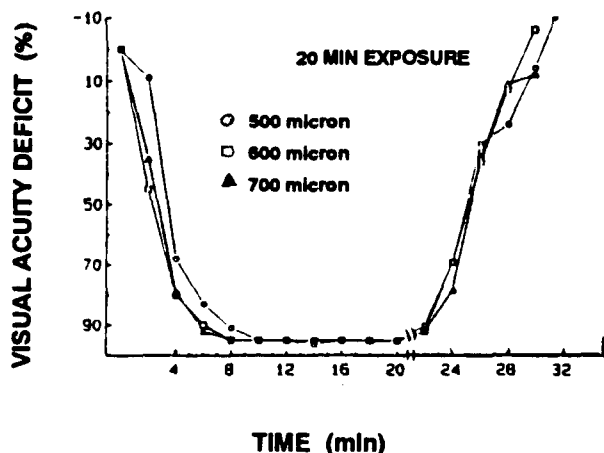ion of the exposure. Immediately after termination of the exposure, the animal's performance increased dramatically, although as with high contrast targets, full recovery was not possible within the initial 15 minute postexposure period.

Changing the size of the exposure area, given that the exposures covered almost the entire visual target, did little to change either the maximum deficit noted or the time for full recovery. Figure 29 shows the effect that retinal spot sizes of 500, 600, and 700 microns have on the ability of an animal to resolve the discriminanda during and immediately after exposure. In this example, the animal was exposed to a 2 uJ laser spot that was presented on-axis (over the discriminanda) for 20 minutes. In this case the animal's ability to detect the critical feature of the visual target decreased significantly (90% decrement from pre-exposure level) and remained depressed as long as the laser irradiation remained on. Typically animals did not increase their false positive rate (responding to gapless rings) and continued to respond to the largest available Landolt rings. They did appear more agitated as demonstrated by their increased body movements and vocalizations. Similar to the examples previously shown, recovery following the exposure was rapid and not dependent upon spot size. In this example the animals were able to regain their lost visual performance in approximately 12 minutes.

The magnitude of the deficit produced by the laser exposure was somewhat dependent upon the power density of the exposure. The impact that various power densities have on the ability of an animal to maintain performance in a visual discrimination task is shown in Figure 30. In this figure, for the lowest power densities employed, the magnitude of the deficit was partial reduced. A 1 nJ exposure, for example, produced a 70 % deficit from the pre-exposure acuity level whereas a 1 or 10 uJ exposure produced a deficit of approximately 95-100%. It should be noted, however, that, at the more intense power levels, the deficits produced represented discriminations of visual targets that almost completely filled the viewing screen. With targets of this size, centering them on the screen and assuring their proper orientation with respect to the position of the laser exposure was

Figure 29. Shifts in visual acuity during and immediately following prolonged laser exposures of differing spot diameters. Visual acuity is plotted as a function of the animal's pre-exposure baseline. Acuity was derived using high contrast, achromatic test targets. The data shown here represent three separate exposure conditions where the animal was exposed to retinal irradiations that covered 500, 600, 700 microns of the central fovea. The exposure duration was 20 minutes. Its onset is indicated at the beginning of each curve and offset at the break in each curve. The overall power density of the exposure 2 uJ.

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extremely difficult. With the higher power densities, the animal's acuity at times dropped below the range of targets that we were able to present. The rate of recovery immediately following the termination of the exposure was again quite rapid indicating the impact of these exposures was only temporary. Slight differences were noted for the various power densities employed although they were not significant. Again, the lowest power densities elicited the most rapid recoveries (4 - 6 minutes) and the highest power densities the slowest (10-12 minutes) recoveries. All animals exposed under these chronic conditions demonstrated complete recovery usually within 20 minutes of the exposure termination and no long term or delay consequences were noted.
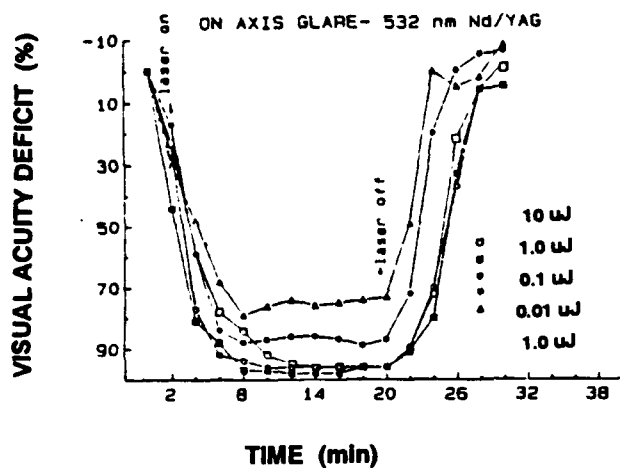

Figure 30. Shifts in visual acuity during and immediately following prolonged laser exposures of differing power densities. Visual acuity is plotted as a function of the animal's pre-exposure baseline. Acuity was derived using high contrast, achromatic test targets. The data shown here represent five different exposure conditions where the animal was exposed to overall retinal irradiations that ranged from 1 nJ to 10 uJ. The irradiation covered a retinal area of approximately 500 microns of the central fovea. The exposure duration was 20 minutes. Its onsets and offsets are indicated. Only one exposure was made per session and several days separated each session.

In the previous examples all exposures were superimposed directly over the critical position on the screen where the animal was centrally fixated and where the position of the gap in the rings were located. Positioning the beam in this location obviously increased the difficulty of the task since, it not only caused

central adaptation, but it also partially or completely eliminated the luminance cues necessary for the correct discrimination. The magnitude of the deficits noted above as well as the frustration (vocalizations and body movements) observed in our subjects support this conclusion. This type of exposure paradigm might be common within the field when detection of the source of laser light is required but does not represent the type of situation where glare from chronic laser viewing might impact visual discrimination. In order to simulate this type of exposure condition the position of the exposure was placed slight off-axis so that the animal could still "look around" the laser spot and detect the critical features of the discriminanda. In this situation the spot was horizontally displaced from the position of gap and depending upon its diameter did not totally obstruct the view of the luminances differences making up the gap in the Landolt ring.

Figure 31 shows the relative advantage of positioning a small diameter, chronic exposure off-axis. In this figure the animal was exposed on two different occasions to a train of laser pulses which, in the midst of the exposure session, was increased in power density. In the initial exposure which was restricted to a 50 micron spot positioned horizontally 2° from the gap in threshold Landolt rings, the animal's
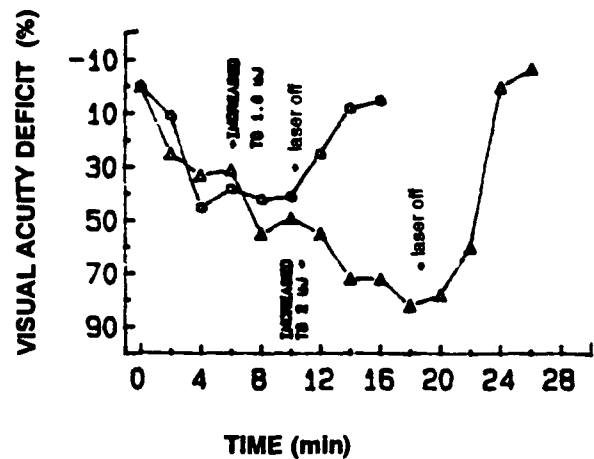
Figure 31. Changes in visual performance during and immediately following prolonged, off-axis exposures. Two separate exposure sessions are shown where the animal was exposed initially to a continuous stream of 0.5 uJ pulses which was increased to either 1.0 uJ or 2 uJ. The 50 micron spot was presented 2° from the discriminanda. The data points were derived from calculations of the animal's acuity for each two minute period. These acuities were plotted as a function of the animal's pre-exposure acuity level.

acuity dropped to approximately 40% of its pre-exposure level and remained at this level until the power density of the exposure was increased. The overall power density of the initial exposure was .5 uJ. In one exposure session this initial power density was increased to 1.0 uJ after six minutes and after another six minutes was terminated. In the initial six minute period acuity decreased by 40% and did not increase with a doubling of the exposure power density. Full recovery from the 12 minutes exposure was rather rapid and in approximately 16 minutes the animal had regained its lost sensitivity. In the second exposure, after 10 minutes at a power density of .5 uJ, the overall power density was increased to 2 uJ and the exposure session terminated 10 minutes later. Initially, this exposure produced an acuity deficit of approximately 50% that was followed by a deficit that peaked at 80% before the animal regained its sensitivity after the laser exposure was terminated. Again in this case the recovery was quite rapid.

Figure 32. Effects of sustained off-axis exposures to visual targets of various contrasts. This animal was exposed on three separate occasions to 0.1 mW, 514 nm laser light that was presented slightly (2°) off-axis. The onset and offset of the approximate 10 minutes exposure is indicated by the dotted lines in this figure. Acuity was measured using darkened targets superimposed on either a low (40%), intermediate (60%), or high (97%) contrast achromatic background.

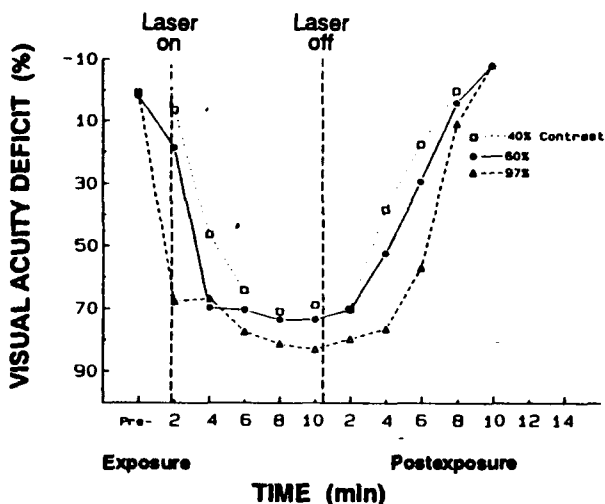Similar to the acute exposure condition, the magnitude of the deficit during and immediately following chronic exposures was somewhat dependent upon the viewing conditions used to access visual performance. In the next two figures the contrast of the images to the background and background wavelength were varied for similar types of exposure conditions. Figure 32 demonstrates the impact the different background contrasts has on the magnitude of the visual deficit. In this example, the animal was tested under three different contrast conditions, 40%, 60, and 97%. Each curve represents a different exposure session where the animal was tested with a different contrast figure. An argon laser presented a continuous irradiation of the screen approximately 2° off-axis. The relatively low energy exposure (0.1 mW) lasted for approximately 10 minutes. Almost immediately after the exposure began visual acuity dropped to 68% its pre-exposure level for low contrast targets, 72% for intermediate contrast targets, and 80% for high contrast targets. The animal's acuities remained at these depressed levels for the duration of the exposure and then rather quickly returned to the animal's pre-exposure baseline once the laser light was terminated. Recovery was always complete within the test session and no permanent loss was noted for the exposure paradigms presented in this example. Generally the slope and extent of the depression of the functions shown are somewhat similar although under these conditions high contrast targets appeared slightly more affected then low contrast targets.

In the next figure (Figure 33) the same exposure conditions were employed but this time the animal was tested under different background wavelength conditions. Three different exposures using three different backgrounds (480 nm, 560 nm, 620 nm) are shown in this figure. Unlike the relatively weak differential that various contrast targets had on the maximum deficit elicited, variations in background wavelength had a significant impact. When the darkened targets were presented against short wavelength backgrounds (480 nm) the overall deficit in acuity to a constantly presented 514 nm off-axis exposure was relatively mild. The animal's acuity dropped to approximately 50% of its pre-exposure level and remained depressed during the entire course of the exposure. Recovery after termination of the exposure was complete within six minutes and no long term deficits were noted in subsequent visual testing. A slightly greater deficit during the course of the exposure and longer recovery was noted when an intermediate wavelength (560 nm) was employed. The most significant drop in acuity was noted when long wavelength (620 nm) targets

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were employed and the magnitude of this deficit (95%) was reminiscent to those observed when using on-axis exposures.
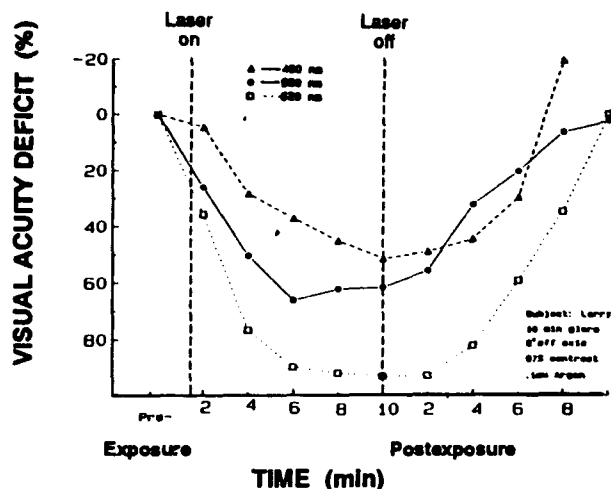

Figure 33. Effects of sustained off-axis exposures to visual targets presented against different wavelength backgrounds. This animal was exposed on three exposed on three separate occasions to 0.1 mW, 514 nm laser light that was presented slightly (2°) off-axis. The onset and offset of the approximate 10 minutes exposure is indicated by the dotted lines in this figure. Acuity was measured using darkened targets superimposed on either a short wavelength (480 nm), intermediate wavelength (560 nm), or long wavelength (620 nm) background.

A number of other exposure paradigms were explored to compare the deficits elicited during and immediately following exposures to various energies and retinal areas of involvement. Regardless of the background conditions used to measure visual performance, or for that matter, the duration or power density of the exposure, the degree of disruption in visual performance was greatest when the exposure was placed directly over the discriminanda and least when it was displaced from the discriminanda. The magnitude of the deficit noted for off-axis was larger than expected and suggests that glare from low level laser irradiation may be an important consideration in predicting performance shifts for those working personnel around laser systems. Equally of concern might be the long term consequences of these exposures on the retina. In this exposure situation the animals were exposed daily to low level,

diffuse irradiation that, because of eye movements, was likely spread across wide regions of the retina. With the energy densities employed, no long term effects were noted but, given the cumulative effects we have previously noted with daily exposures of a shorter duration but higher power density, it is likely that longer duration exposures or higher power densities in the current paradigm would have eventually produced longer term, or even permanent, functional decrements in visual performance.

DISCUSSION

The methodology developed during this and previous studies (36) appears appropriate for producing foveal exposures in awake, task-oriented animals. The magnitude of the visual deficits produced and their relationships to the various exposure parameters studied, including power density, spot size, and position on the retina, support this notion. This methodology is unique in that it allows not only for the accurate placement of laser beam on the retina without the need for anesthesia but it also allows for the determination of visual performance during and immediately following laser exposure. The measurement of visual acuity during and immediately following exposure is critical in deriving what might happen to the ability of a soldier to complete a visually-guided mission after being exposed to laser light. This procedure also allows for assessments of power densities at or below the point where significant permanent or long term shifts in visual performance can be observed. Verification of the transitional zone between temporary and permanent functional changes will allow for the establishment of safety standards that on one hand are not overly conservative and but on the other hand take into account transient changes which might disrupt retinal functioning. Overly conservative standards might limit the usefulness of the laser as a optical device while more liberal standards without behavioral documentation ignore the primary purpose of the human visual system.

This study continues to confirm the appropriateness of the rhesus as an experimental model for predicting human performance changes following laser exposure. The sensitivity of this species to light and its fundamental decision-making ability to use information derived from the visual system, is essentially the same as that of the human observer. The

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changes in acuity to variations in luminance, contrast, and wavelength under baseline conditions compare nicely to human data collected in the same apparatus. Slight changes in maximum acuity between the two species at the extremes of the luminance scale can be primarily accounted for by optical factors. An enlarged pupil in the rhesus increases light scatter for maximum light conditions and increases light absorption at lowest luminance levels. Slight differences in the number of photoreceptors and the distribution of color pigments within the macula may have produced the observed differences in the spectral acuity noted for the two species. These minor deviations can easily be documented and adjustments made when determining human susceptibility to laser light or when predicting lost visual functioning following exposure.

The training procedure developed for this project appears adequate to motivate the animal to perform even during periods when his sensitivity has been greatly reduced as a result of the laser irradiation. The data presented in this report confirm that our animals maintained their vigilance even during prolonged foveal exposures. Furthermore, our animals developed constructive strategies to utilize normally less sensitive retinal regions (parafoveal or peripheral zones) to maintain their maximum visual acuity under the existing light conditions. Even when exposed to intense light capable of fully beaching or damaging the photoreceptors and their neural interconnections, our animals appeared to be able to quickly shift their eye position to utilize unexposed portions of their retina. The up-and-down procedure that was used to measure visual thresholds proved to be a rapid and reliable means of accessing ongoing visual sensitivity. This technique was originally developed to rapidly measure auditory thresholds and appears particularly well suited for any perceptual experiment where vigilance and speed are mandated. The difficult of this visual task required continuous central fixation which helped to assure proper eye position for foveal exposures.

At the onset of this study several hypotheses were advanced. First, it was proposed that light-induced damage to the retina should not only disrupt retinal physiology but also should adversely affect visual functioning. Damage to areas inside the fovea should have more severe effects on visual acuity and color vision while exposure to the peripheral retina may disrupt scotopic vision but should have a lesser effect on fine visual acuity. Clearly, our initial results support this notion although off-axis exposures have been shown to have a greater disruptive effect on foveal functioning than might otherwise have been expected. The changes in maximum sensitivity to off-axis exposures, however, appeared more temporary in nature than those noted for similar foveal exposures. This suggests that the deficits produced may be more the result of glare or distraction rather than having a clear physiological significance. Never-the-less the impact that chronic off-axis exposures have could dramatically alter visual performance by creating distractive eye movements and prolonged afterimages in the areas initially unaffected by the exposure.

Second, we proposed that the number of foveal photoreceptors altered should affect the magnitude of the visual deficit elicited. A single punctate lesion involving only a limited number of photoreceptors should have little consequence on overall visual acuity, but more numerous lesions created by multiple exposures should eventually summate to adversely affect any discrimination requiring fine resolution. Our repetitive exposure data demonstrates that with successive exposure it becomes increasingly difficult for an animal to "look" around affected regions and still maintain a consistent and elevated performance level. Eventually, these small punctate lesions produce a behavioral deficit similar in scope to that observed when large areas are irradiated. Except for an initial dazzle effect, isolated punctate lesions should have little impact on the resolution of simple targets provided the animal has the time and ability to scan the visual field. Increasing the complexity of the visual task or decreasing the time allowed for fixation might result in observable visual deficits that were not possible in this study. The use of more complex targets in the future should be considered.

Third, we proposed that isolated punctate lesions of the fovea would be expected to increase discrimination errors as critical features of briefly presented targets fell on damaged regions. Our results to date demonstrate an increase in within and between session variability following exposures that "damage" only limited areas (<50 microns) of the fovea. Associated with this increased variability in baseline sensitivity is a change in the animal's false positive rate as well as increases in the time it takes the animal to respond.

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Fourth, should the energy of exposure, regardless of its retina spot size, produce an edema within or around surrounding the exposed tissue, at least a temporary visual deficit should be noted. An edema should alter photoreceptor orientation, spacing, and functioning and thereby temporarily create disruptions in visual performance that, based on the size of the lesion, would otherwise not be expected. Our results demonstrate that often within several minutes of an intense, punctate exposure a temporary recovery in visual performance occurred followed by a significant deficit either in the same or subsequent test sessions. This deficit was often greatest the day after exposure and some partial recovery was noted over the next several days or weeks of postexposure testing. This type of initially delayed and often variable deficit could have been the result of changing conditions within the edema.

Furthermore, hemorrhages within the retina should result in a clouding of the ocular media thereby increasing light scatter, creating a blurred image, and reducing the fine resolution capabilities of the fovea. Our behavioral data have demonstrated delayed effects and effects that vary considerably immediately after exposure to intense, but small spot exposures. Given the normal stability of our data prior to exposure and following low level exposures, it is certainly possible that these behavioral changes were associated with changes in the optical properties of the eye due to hemorrhages.

A fifth hypothesis proposed that, independent of any transient or permanent morphological change, visual acuity could easily be disrupted by a dazzle effect from less intense laser exposure. These effects should be immediate but transien* As previously mentioned this "dazzle" effect can occur for low-level foveal exposures or for intense off-axis exposures which leave the foveal functioning theoretically unaltered. These effects have been shown to quickly dissipate once the exposure is terminated but never-the-less must be considered when predicting human performance susceptibility to laser irradiation.

Sixth, we proposed that the nature of the observed loss in visual sensitivity should be dependent upon the discrimination task used. Changes in the contrast of the target or the wavelength of the background elicit differential effects. Chromatic targets appear more sensitive in depicting changes in postexposure visual functioning than do achromatic targets as do low contrast targets in comparison to high contrast targets.

In addition, the wavelength and repetition rate of the laser pulses may interact with both the type and magnitude of damage elicited and these two factors should relate directly to changes in visual performance. We extensively explored the impact that repetitive pulses presented in rapid succession have on the magnitude of the elicited deficit and duration for full recovery. We also explored the temporal summation of pulses by presenting either a single pulse or multiple pulses equated for power density. Multiple pulses were slightly more effective in producing shifts in visual performance than single pulses of comparable total energy although the difference was neither significant nor stable across different energy parameters. Primary reason that multiple pulses should be more effective in eliciting a deficit is because they should involve larger retinal areas due to the spreading of the laser light across the retina by eye movements. Given the relatively short duration of the pulses to begin with, any condition which spreads the energy across a larger area of the fovea should produce measurable results.

The magnitude of the deficits elicited by our procedures was reminiscent of the maximum, permanent deficits observed in other studies where more intense irradiation was placed directly onto the fovea using anesthesia to limit eye and body movements. Typically on-axis exposures produced an initial deficit of 20-60% from the animal's pre-established baseline although both the duration of the exposure (number of pulses) as well as the retinal spot size were significant determinants of the magnitude of this deficit. The time required for recovery from even relatively low power densities (densities below ED_{50}) used in our studies was beyond the normal recovery times calculated for a full bleach of foveal cones suggesting that our results implicate abnormal or non-photochemical changes may have been involved. The time required for full recovery or the likelihood of recovery from the laser irradiation was critically dependent upon the overall power density of the exposure. Relatively low power densities produced only transient effects that had little or no long term consequences. Some cumulative influences from daily or chronic exposures were noted for exposures which initially produced only a transient decrement, although such cumulative interactions were difficult to document.

Not all exposures produced an immediate shift in visual acuity. This was especially true when we employed relatively brief (15 nsec), single pulses that produced only a minimal (<50 microns) retinal spot. Several factors could contribute to this lack of visual deficit in spite of the fact that the energy of the exposure was still sufficient to fully bleach any photoreceptor that might have been exposed. First, involuntary or reinitiated voluntary eye movements could have resulted in irradiation of extrafoveal areas instead of foveal areas. The irradiation of these peripheral areas should produce little if any shift in maximal acuity since only foveal areas are normally involved in the detection of fine spatial detail. It is also possible that lid closures, especially when subthreshold energy levels were employed, might have resulted in reduced foveal involvement and hence produced only minimal shifts in visual acuity immediately following exposure. An alternative possibility is that the exposure, while relatively intense in nature, elicited damage only in a relatively small region of the retina. Such a consequence would make it possible for the animal to "look" around the lesioned area and use functionally active zones that previously had not been adversely affected by exposure. In those exposures that did produce a visual decrement, our animals maintained vigilance and continued to respond, despite their often reduced visual sensitivity supporting the need for a task which requires the animal to maintain vigilance even while partially disabled. Further, our data suggest that our animals did not initially change their detection criterion (beta value) as indicated by their unchanged false alarm rate for targets below their new threshold level. What did change was the animal's sensitivity (d') to resolve this spatial task. The lack of a total functional impairment implies that the paradigm significantly motivated the animals to learn to employ unexposed retinal areas to make the required discrimination even if this meant looking off-axis at the critical features of the targets. For the single pulse condition using minimal diameter spots, this often meant "looking" around or through the minimally disrupted region of the fovea. For the multiple pulse condition or for large diameter spots it would have meant that the animal must have employed regions outside the fovea for detection the critical feature of the target. The magnitude of the initial deficit and its dependence on beam diameter supports this parafoveal hypothesis.

The effects of eye movements and position has not be adequately explored. We have noted that relatively large deficits (50% to 90%) can be produced by even our minimal diameter beams (50 micron spot on the retina) when the exposure duration is set for 100 msec or when the animal receives multiple, brief exposures of sufficient power. While these brief durations prevented the animal from voluntarily moving his eye away from the bright light source they did not eliminate the rapid, irregular involuntary eye movements naturally occurring during any fixation. This type of eye movement smears any image across a larger retinal region than would be calculated purely on the basis of spot size. This might explain why even relatively small diameter retinal exposures (50 microns) produced a somewhat larger and longer decrement in postexposure visual acuity than might otherwise be expected.

Without eye movements or with shorter duration exposures one would not expect to observe any shift in postexposure acuity when minimal diameter (50 microns) exposures are used. Such was the case even when the power density was above the ED_{50} level but exposure duration was limited to 15 nsec. In this study we have shown that with very short duration exposures (<50 msec) little or no observed temporary acuity deficits were observed regardless of the energy density employed. In those cases where the energy density was significantly above the ED_{50} level and when physical damage was notably restricted to a small retinal region one might expect the animal's performance to be more erratic as he must learn to "look" around damaged regions. This clearly was confirmed in our postexposure testing. Multiple exposures, on the other hand, that were either close or far in time from each other should eventually produce a consistent and long term drop in postexposure acuity as the lesion sites increasingly spread across the fovea. This too was confirmed in our initial investigations.

The notion that the region of retinal involvement, whether as the result of changes in beam diameter or exposure duration, has a significant effect on the magnitude and duration of any observed acuity deficit, was also supported by our off-axis experiments. Intentionally positioning the beam away from the animal's point of central fixation (off-axis) decreased both the magnitude and duration of any elicited acuity deficits. We have begun to measure baseline sensitivities of more peripheral regions of the

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retina by placing the exposing beam at various degrees of eccentricity.

For those foveal exposures which produced only transient changes in visual acuity, the duration for full photopic recovery was often significantly longer than that typically observed in human psychophysical studies where incoherent light produced a state of full beaching. The average recovery duration for our transient effect was 20 minutes, and this time was much longer than the 3 to 5 min adaptation time characteristic of other full bleach photopic studies. This relatively long recovery time suggests that aberrant photochemical changes and/or neural processing within the fovea were operating, which required a longer than usual time to reverse.

In those exposures where recovery was not complete within the 45 minute test session, partial recovery was often observed in subsequent postexposure sessions often days or even weeks following the initial exposure. These animals often experienced a greater deficit during the early stages of the recovery process which could have been the result of hemorrhages clouding the ocular media and edema altering photoreceptor orientations. As time passed, these physical alterations would naturally become reduced. Their changes in time might explain the changes noted in our behavioral study. The increased variability of performance following exposure might also be explained by differential strategies used by the animal to employ unaffected retinal regions. As the animal learned to consistently employ the less sensitive parafoveal regions, his visual performance should not only improve but also show less within and between session variability.

Our data continues to support the notion that the nature of the visual task can significantly influence one's u\ ction of changes in the visual system follow.] laser exposure. Chromatic and low contrast targets appeared more affected by laser irradiation than did other types of visual displays. This suggests that these targets provide a more sensitive measure of retinal disruption than do high contrast, achromatic targets. It also suggests that achromatic photopic viewing conditions might be more appropriate in those situations where laser exposure has occurred and visual performance after exposure must be maintained.

Future behavioral studies should consider employing more spatially complex visual targets differing in spatial frequencies and contrast levels to more precisely reflect real life exposure conditions. Unfortunately the complexity of most training and testing procedures makes such analyses more time consuming especially when examining the transitional zone between temporary and permanent functional losses. Our current methodology for exposure requires a spatially simple task to be able to specify where the animal is fixated. The use of more complex targets that have multiple fixation points requires a means of measuring and predicting the animal's eye movements. The addition of an eye tractor would not only aid in this determination but would also allow for the one to observe the eye movement strategies used by our animals, once exposed, to maintain their perceptual vigilance. Behavioral research of the type described are the only way to accurately predict postexposure visual capacities and ultimately may provide more realistic standards upon which to rate the potential hazards from laser irradiation.

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ADDENDUM TO USAMRDC FINAL REPORT

CONTRACT # DAMD17-83-C-3172

DAMD17-88-C-8032

ADDENDUM A: PUBLICATIONS AND PRESENTATIONS RESULTING FROM THIS RESEARCH

PUBLICATIONS

Robbins, D.O., Zwick, H. and Leedy, M. Transient and permanent effects of small and large diameter retinal exposures on rhesus spatial vision. Neuroscience Abstracts. 10 (1984).

Robbins, D.O., Zwick, H., Leedy, M. and Stearns, G. An acute restraint device for rhesus monkeys. Laboratory Animal Science (1984).

Zwick, H., Sherman, M., and Robbins, D.O. Computer image analysis of laser induced punctate lesions. Neuroscience Abstracts. 11 (1985).

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Robbins, D.O. Functional Assessment of Laser Irradiation. Final Report DAMD17-75-C-5008 and DAMD17-81-C-1065 Contracts with the US Army Medical Research & Development Command, Fort Detrick, MD March 1988

Robbins, D.O. Analysis of the Effects of High-Energy Q-Switched Laser Pulses on the Primate Retina. Final Report, DAMD17-83-C-3172 Contract with the US Army Medical Research & Development Command, Fort Detrick, MD October 1988

Robbins, D.O., Zwick, H., Nawim, M.S., and Long, R.C. Visual Effects of Transient and Prolonged Small Spot Laser Exposures. Neuroscience Abstracts. 14 (1988).

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PAPERS DELIVERED AT PROFESSIONAL MEETINGS:

Robbins, D.O., Zwick, H. and Leedy, M. Transient and permanent effects of small and large diameter exposures on rhesus spatial vision. Paper presented at the Neuroscience Annual Meeting, Los Angeles, CA, October 1984.

Zwick, H., Sherman, M., and Robbins, D.O. Computer image analysis of laser induced punctate lesions. Paper presented at the Neuroscience Annual Meetings, Dallas, TX, October 1985.

Robbins, D.O., Long, R.C., and Zwick, H. Q-switched Nd/YAG exposures: effects in a primate retina. Paper presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, FL, May 1986.

Zwick, H., Bloom, K, Robbins, D.O. Long Term Changes Associated with Punctate Lesions. Paper presented at the ninth IRCGCVD Symposium on Color Vision Deficiency, Annapolis, MD, July 1987.

Robbins, D.O., Zwick, H., and Long, R.C. Relationship between small punctate lesions and immediate shifts in visual acuity in the primate retina. Paper presented at the annual meetings of the Society for Neuroscience, New Orleans, LA, November 1987.

Robbins, D.O., Zwick, H., Nawim, M.S., and Long, R.C. Visual Effects of Transient and Prolonged Small Spot Laser Exposures. Paper presented at the meetings of the Society for Neuroscience, Toronto, Canada, November, 1988.

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Gunzenhauser, J., Zwick, H., Molchany, J., and Robbins, D.O. Comparison of visual recognition thresholds for normal and degraded images. Paper to be presented at the Annual Meetings of the Society for Neuroscience, New Orleans, LA, November 1991.

ADDENDUM B: PERSONS RECEIVING STIPEND FOR THIS RESEARCH

Salaried Staff: [1]

David O. Robbins, Ph.D   Principal Investigator
Thomas Dillman, Ph.D.   Research Physicist
Ron Bell, D.V.M.   Veterinarian

Mitz Leedy, Ph.D.   Research Associate
Regina Long, M.A.   Research Associate

Lynne Mecum, B.A.   Research Assistant
Robert Pardee, B.A.   Computer programmer
Gina Olimpio, B.A.   Research Assistant
N. Zwumwalde, B.A.   Research Assistant

Hourly Staff:

Robert Pardee, B.A.   Computer Programmer
Mary Ann Nelson   Research/Data Assistant

Student Labor: [2] Minimum wage staff

Natasha Shah   Michael Trimble
John Wiebe   Hasan Imam
Jody Gordon   Joel Peterson
Jonathan Miller   Kathryn McDonnell
Tammy Daily   Sonya Hulteen

No graduate degrees resulted from this research support

[1] *Only one Research Associate/Assistant was on the payroll at any one time.*

[2] *Students were in charge of animal maintainence which included the feeding of animals and the cleaning of their cages. Other students during this time were also assigned this task but their salaries were charged to other university accounts.*